COGNITIVE CONTROL UNDER INCENTIVES IN DEVELOPMENT AND ADOLESCENT MOOD AND ANXIETY DISORDERS

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SUMMARY

Background: Adolescence is a developmental time span not only characterized by a profound improvement in cognitive and physical capacities, but also by an increase in affective turmoil such as emotional lability and impulsivity, and a marked increase in the prevalence of severe and chronic psychiatric disorders such as mood and anxiety disorders. Recent findings from the field of Developmental Cognitive Neuroscience indicate that adolescent difficulties in affect regulation may in part result from maturational transitions in brain architecture and organization during this age span, leading to a temporary dysbalance between neural systems mediating regulatory-cognitive control and those mediating affective states. Moreover, findings from neuroimaging and neuropsychological studies suggest that this dysbalance in neural systems may in some instances transcend into adulthood, conferring risk for suffering from affective disorders beyond the time of adolescence. A better understanding of the interaction between cognition and affect during adolescence by neuroscience-based methods thus may further advance the understanding of normative adolescent behavior and possibly of the pathophysiology of mood and anxiety disorders.

Methods: Behaviorally, differences in the interplay of regulatory-cognitive and affective brain functions between healthy adolescents, adolescents with affective disorders and adults could be reflected in motivated behaviors and/or cognitive control processes such as attention allocation or inhibitory control within reward-related contexts. To test this hypothesis, a new eye movement task, the reward saccade task (RST), was developed to assess the influence of three different incentive conditions on eye movements of differing cognitive demand in 30 adults, 32 adolescents, 16 adolescents with an anxiety disorder, and 12 adolescents with major depressive disorder (MDD). Specifically, subjects were asked to either look at a peripherally appearing target (prosaccade instruction) or away from it (antisaccade instruction), and depending on performance accuracy they could either win or not win a monetary reward, lose or avoid losing a monetary punishment, or were informed on task performance without monetary implications. While prosaccades are simple, visually-guided eye movements, antisaccades are internally-guided eye movements that involve several higher order cognitive processes such as response inhibition (suppress the reflex to look at the target) and attention allocation towards a location void of any visual cue. The investigation of saccadic eye movements is an apt neuroscience-based method since saccadic eye movements are easily measurable with high temporal resolution, can be integrated in different paradigms of differing cognitive demand such as the antisaccade and prosaccade paradigm, are sensitive to inventive manipulation and have been mapped in extensive animal and human research onto precise neural circuits and thus can inform about the functional state of these circuits.

For analysis, the influence of the three different incentive conditions was evaluated for global task performance measures (i.e. proportion of correct and erroneous responses per saccade type) and dynamic task performance measures (latency, peak velocity, duration and amplitude for each type of

saccadic response). Moreover, the influence of feedback notification on pupil diameter and fixation duration was analyzed. Performance was compared between age groups (developmental study) and between clinical states (clinical study).

Results Developmental study: Adolescents had compared to adults more difficulty performing the task, i.e. they committed more errors on antisaccade trials and had longer latencies before performance of a correct antisaccade. Incentives modulated global task performance in both age groups in a similar fashion; however, this influence differed between saccade types: While for antisaccades the prospect of winning money and threat of losing money both improved performance accuracy as compared to a non-incentive condition, for visually-guided saccades there was an improvement of performance only for the prospect of a monetary reward, but not of performance under the threat of monetary punishment, as compared to a non-incentive condition. For the adolescent, but not the adult group, the influence of incentives was also reflected in dynamic saccade measures for visually-guided saccades (correct prosaccades, antisaccade direction errors), but not internally-guided correct antisaccades. Specifically, adolescents had increased latency and peak velocity for direction errors under prospect of monetary reward and increased latency and peak velocity for prosaccades under the prospect of monetary punishment.

Results Clinical study: Controls and patients did not differ in global and dynamic task performance parameters per se, but in the modulation of task parameters by incentives. While adolescents from the control group showed an improvement of task performance by incentives (i.e. by potential reward and threat of punishment) under high, but not low cognitive control, patients with MDD failed to optimize financial pay-off regardless of saccade type as evidenced by a lack of within-group improvement of global accuracy by incentives. In terms of dynamic performance measures, patients with MDD contrary to controls exhibited an influence of incentives for internally-guided antisaccades, but not for visually-guided prosaccades and antisaccade direction errors. Finally, patients with MDD showed higher attentional engagement (i.e. longer fixation duration) for negative feedback, as compared to controls. Patients with an anxiety disorder showed an attentional bias for threats as indicated by shorter saccade latency for prosaccade trials and a higher proportion of corrected direction errors under the punishment condition. Overall, performance pattern of patients with anxiety indicated higher arousal as revealed by increased peak velocity regardless of incentive condition, as compared to controls.

Conclusions: The findings from this exploratory study employing a new eye movement task suggest that incentives modulate different aspects of cognitive control processes in adults, psychiatrically healthy adolescents and adolescents with a mood and anxiety disorder. The overall pattern of incentive-related modulation across development indicates improvement of task performance by incentives under high cognitive control as was the case for adults and for correct antisaccades (i.e. better global performance under incentives, but no influence of incentives on dynamic performance measures). In contrast, under low cognitive control as was the case for adolescents and for visually-guided saccades, task performance was more strongly dominated by incentives, with deterioration of

performance where there was a conflict between motivational (i.e. approach a reward) and cognitive task demands (look away from a reward cue). For the clinical study, findings indicate that disease-typic behaviors and cognitive biases reported for adults with mood and anxiety disorders can already be found in adolescents afflicted by these disorders on the RST. While the differences between anxious and control adolescents in task performance may in part be due to different levels of arousal, the differences between depressed and control adolescents may reflect a perturbation in the neural circuit specifically underlying internally-guided saccades. These findings need to be replicated with greater patient samples; however, they suggest that the study of reward-related information processing in adolescent mood and anxiety disorders may contribute to a better understanding of the pathophysiology of these disorders and that the RST can be used to probe reward-related information processing from a developmental and clinical perspective, preferably in combination with functional neuroimaging methods.

ZUSAMMENFASSUNG

Hintergrund: Die Adoleszenz ist derjenige Zeitabschnitt der menschlichen Entwicklung, in welchem der Heranwachsende seine körperliche und geistige Reife erlangt. Bei vielen Adoleszenten ist dieser Reifungsprozess begleitet durch Schwierigkeiten in der Affektregulation, wie zum Beispiel vermehrt auftretenden Stimmungsschwankungen, Impulsdurchbrüchen oder gar der Entwicklung einer ab diesem Lebensabschnitt markant häufiger zu beobachtenden affektiven Störung. Neuere Befunde aus dem Gebiet der Kognitiven Neurowissenschaften weisen darauf hin, dass diese für die Adoleszenz relativ typischen Störungen in der Affektregulation durch reifungsbedingte Entwicklungsprozesse im Gehirn mitverursacht werden können, die zu einem vorübergehenden Ungleichgewicht zwischen regulativ-kognitiven und affektiven Hirnfunktionen führen. Ein ähnliches Ungleichgewicht zwischen regulativ-kognitiven und affektiven Hirnfunktionen wurde mittels funktionaler Bildgebung und neuropsychologischen Studien auch für Erwachsene mit einer affektiven Störung berichtet. Die Erforschung des Zusammenspiels zwischen kognitiver Kontrolle und Affekt in der Adoleszenz mittels neurowissenschaftlichen Mitteln könnte somit zu einem besseren Verständnis der neurobiologischen Ursachen sowohl normativer adoleszenter Verhaltensweisen, als auch der Entstehung psychiatrischer Erkrankungen wie Depressionen und Angststörungen beitragen.

Methoden: Unterschiede im Zusammenspiel von kognitiver Kontrolle und Affekt zwischen gesunden Jugendlichen, solchen mit emotionalen Schwierigkeiten und gesunden Erwachsenen könnten sich im Appetenzverhalten und/oder der Aufmerksamkeitssteuerung unter Anreizen widerspiegeln. Um dies zu untersuchen, wurde eine neue Augenbewegungsaufgabe, die reward saccade task (RST) entwickelt, in welcher Augenbewegungen gemessen wurden unter verschiedenen kognitiven Schwierigkeitsgraden und unter drei verschiedenen finanziellen Anreizbedingungen bei 30 Erwachsenen, 32 Jugendlichen, 16 Jugendlichen mit einer Angststörung und 12 Jugendlichen mit einer majoren depressiven Erkrankung (MDD). Konkret wurden die Versuchspersonen gebeten, entweder auf einen in der visuellen Peripherie erscheinenden Reiz zu blicken (Prosakkaden-Instruktion) oder in dessen gegenüberliegende Richtung (Antisakkaden-Instruktion), und wurden je nach Richtigkeit der Bewegung finanziell belohnt oder nicht belohnt, finanziell bestraft oder nicht bestraft, oder erhielten Rückmeldung über ihre Leistung ohne finanzielle Folgen. Während Prosakkaden einfache, visuell-geführte Augenbewegungen sind, handelt es sich bei Antisakkaden um intern-gesteuerte Augenbewegungen, welche verschiedene Prozesse kognitiver Kontrolle beanspruchen wie z.B. die Unterdrückung des Reflexes, auf einen peripheren Reiz zu blicken, und die Ausrichtung der visuellen Aufmerksamkeit auf einen Ort in der Peripherie ohne visuelles Ziel. Sakkaden eignen sich als neurowissenschaftliche Methode, weil sie einfach und genau zu messen sind, in kognitiv verschieden anspruchsvolle Paradigma wie z.B. der Pro- oder Antisakkaden-Instruktion eingebettet werden können, sensibel auf Anreize reagieren und weil ihre neurobiologischen Grundlagen durch frühere Untersuchungen an Menschen und Primaten genau bekannt sind. Letzteres erlaubt es, Rückschlüsse von der Ausprägung einzelner Sakkadenparameter auf die Funktion bestimmter neuronaler Regionen und Systeme zu ziehen.

Statistisch analysiert wurde, wie sich die drei verschiedenen Anreizbedingungen auf die globale Leistung in der RST (Anteil an korrekten und inkorrekten Augenbewegungen pro Sakkaden-Instruktion), als auch auf dynamische Indikatoren der einzelnen Augenbewegungen auswirken (Latenz, Geschwindigkeit, Dauer und Grösse der Augenbewegung). Zudem wurde die Auswirkung der Rückmeldung über die Richtigkeit einzelner Aufgabendurchgänge auf die Pupillengrösse und die Dauer des ruhenden Blickes auf diese Rückmeldung bestimmt. Die Ergebnisse wurden verglichen zwischen den beiden gesunden Altersgruppen (Entwicklungsstudie) sowie zwischen den drei adoleszenten Gruppen (klinische Studie).

Ergebnisse der Entwicklungsstudie: Jugendliche hatten im Vergleich zu Erwachsenen grössere Schwierigkeiten in der RST, d.h. sie begingen mehr Fehler während der Antisakkaden-Instruktion und führten korrekte Antisakkaden mit grösserer Latenz aus als Erwachsene. Anreize beeinflussten die globale Leistung in beiden Altersgruppen auf ähnliche Weise, ihr Einfluss variierte jedoch zwischen den beiden Sakkaden-Typen: Während für die Antisakkaden-Instruktion mehr richtige Augenbewegungen unter Erwartung finanzieller Belohnung bzw. unter Androhung finanzieller Bestrafung erfolgten als unter der finanziell neutralen Bedingung, war die globale Leistung in der Prosakkaden-Instruktion im Vergleich zur neutralen Bedingung nur unter Erwartung finanzieller Belohnung, nicht aber unter Androhung finanzieller Bestrafung erhöht. Die dynamischen Parameter der einzelnen Sakkaden unterschieden sich bei Erwachsenen nicht zwischen den verschiedenen Anreizbedingungen. Bei Jugendlichen variierte die Ausprägung der dynamischen Parameter zwischen den verschiedenen Anreizbedingungen in Abhängigkeit der kognitiven Kontrolle, d.h. sie war nur zu beobachten für visuell-geführte Augenbewegungen (d.h. für korrekt ausgeführte Prosakkaden und für Richtungsfehler bei der Antisakkaden-Instruktion), nicht aber für intern-gesteuerte Augenbewegungen (d.h. für korrekte Antisakkaden). Konkret initiierten Jugendliche Prosakkaden langsamer und mit höherer Geschwindigkeit unter Androhung einer finanziellen Bestrafung und Antisakkaden-Richtungsfehler langsamer und mit höherer Geschwindigkeit unter Erwartung einer finanziellen Belohnung.

Ergebnisse der klinischen Studie: Die Jugendlichen der drei Gruppen zeigten deutliche Unterschiede im Einfluss von Anreizen auf die Leistung in der RST. Während Jugendliche aus der Kontrollgruppe eine verbesserte Leistung unter finanziellen Anreizen aufwiesen, insbesondere bei hoher kognitiver Kontrolle (d.h. für korrekte Antisakkaden), konnten Patienten mit einer MDD den finanziellen Ertrag nicht optimieren, d.h. sie zeigten keine Verbesserung der globalen Leistung unter finanziellen Anreizen unabhängig vom Sakkadentyp. Bei dynamischen Parametern zeigten Patienten mit einer MDD im Gegensatz zu gesunden Kontrollpersonen einen Einfluss der verschiedenen Anreizbedingungen auf intern-gesteuerte, nicht aber visuell-geführte Augenbewegungen (d.h. für korrekte Antisakkaden, nicht aber für Prosakkaden oder Richtungsfehler). Schliesslich unterschieden sich Patienten mit einer MDD von gesunden Kontrollpersonen durch ihre Reaktion auf negative Rückmeldungen (d.h. Rückmeldung über finanziellen Verlust), welche sie länger anblickten. Patienten mit Angststörungen lenkten ihre Aufmerksamkeit vermehrt auf negative Reize, d.h. sie hatten kürzere Reaktionszeiten für Prosakkaden, und korrigierten mehr Richtungsfehler bei Androhung auf finanzielle Bestrafung im Vergleich zu den gesunden Kontrollpersonen. Zudem führten sie verglichen mit Kontrollpersonen kor-

rekte Augenbewegungen unabhängig von der Anreizbedingung schneller aus, was auf eine allgemein erhöhte Erregung hinweist.

Schlussfolgerung: Die Befunde dieser explorativen Studie mit einer neuen Augenbewegungsaufgabe weisen darauf hin, dass Anreize verschiedene Aspekte der kognitiven Kontrolle bei Erwachsenen, gesunden Jugendlichen, und Jugendlichen mit einer Angst- oder depressiven Erkrankung beeinflussen. Die Befunde der Entwicklungsstudie zeigen, dass bei hoher kognitiver Kontrolle wie sie bei Erwachsenen und für korrekte Antisakkaden gegeben war, die Leistung in der RST durch Anreize unterstützt wird (mehr korrekte Bewegungen, aber geringerer Einfluss von Anreizen auf dynamische Augenbewegungsparameter). Bei geringer kognitiver Kontrolle, wie sie bei Jugendlichen und bei Prosakkaden und Richtungsfehlern auftritt, üben Anreize hingegen einen stärker dominierenden Einfluss auf die Ausübung der RST aus wie bei hoher kognitiver Kontrolle, und verschlechtern die Leistung dort, wo ein Konflikt zwischen motivationalen Bedürfnissen (z.B. einen appetitiven Reiz anblicken) und kognitiven Ansprüchen (in die entgegengesetzte Richtung eines appetitiven Reizes blicken) in der Aufgabe besteht. Die Befunde der klinischen Studie zeigen, dass kognitive Verzerrungen und Verhaltensweisen, wie sie bei Erwachsenen mit Angst- und affektiven Störungen im Zusammenhang mit affektiven Reizen berichtet wurden, bereits bei Jugendlichen mit diesen Störungen in der RST zu beobachten sind. Die Unterschiede zu den Kontrollpersonen scheinen bei Jugendlichen mit einer Angststörung massgeblich durch ein erhöhtes Erregungsniveau hervorgerufen worden zu sein. Bei Jugendlichen mit einer MDD weisen die Befunde hingegen auf eine Dysfunktion im neuronalen Schaltkreis hin, welcher intern-gesteuerten Sakkaden zugrunde liegt. Diese Befunde müssen in grösseren Patienten-Stichproben repliziert werden, untermauern soweit aber den Nutzen der Untersuchung von Anreizen auf die kognitive Kontrolle für die Erforschung der Pathophysiologie von affektiven Störungen sowie die Eignung der RST als Paradigma zur Messung solcher Einflüsse, vorzugsweise in Kombination mit funktionaler Bildgebung.

I. INTRODUCTION

In the last couple of years, the meanders of adolescents have gained wide resonance in the public media attention and in political discussions. In particular youth delinquency – i.e. violent attacks against passers-by, sexual assaults towards girls, reckless driving - but also an increase in consumption-oriented behaviors without regard for the long-term consequences - i.e. skyrocketing mobile phone costs, peer pressure to dress in certain expensive fashion trends, an increase in prevalence of binge drinking to mention just a few examples – have become widely discussed topics. Similarly, counteractive measures are hotly debated and an apt platform for politicians to take up a position on family and general social policies in a postmodern society. Another, similarly disturbing and increasingly recognized characteristic of adolescent behavioral propensities besides impulsivity is the emotional turmoil at this age span, beginning from frequent mood swings to a stark increase in the prevalence of clinically relevant negative mood states such as depression and anxiety. While for most adolescents these mood swings are transitory, for some it is the beginning of a lifelong battle with affective disorders.

Yet, although the “storm and stress” of adolescence currently is receiving increased attention, it is not at all a new phenomenon. As reviewed by Arnett (1999, pg. 317) already Aristotle noted that “youth are heated by nature as drunken men by wine”, and Socrates characterized youth as inclined “to contradict their parents” and “tyrannize their teachers”. Shakespeare not randomly put the age of Juliet of his play *Romeo and Juliet* to a fragile 13 years old. And also Goethe addressed adolescent storm and stress in his novel *The Sorrows of Young Werther* in which a young man commits suicide in despair over an unfulfilled love. Moreover, risk- and sensation-seeking behavior is not limited to human adolescents, but indeed to adolescents in many species, presumably to serve the evolutionary purpose of preventing incest and acquire new territories and behaviors (Spear, 2000). An excerpt from a recent interview with three teenage girls aged 16 published on the 25th of June 2008 by the Swiss News Magazine “Weltwoche” nicely underscores this notion. Asked on the differences between teenagers and adults, one girl replied: “I don’t want to plan everything. Moreover, we rarely expect the worst. To do so, we lack the experience. This is also the reason, why we are more risk-seeking than older people. I think we have to make our own experiences. Otherwise we will never learn.” So, considering these facts, there seems to be a normative/adaptive reason for adolescent behavioral propensities that, however, in conjunction with the temptations available in a postmodern world imposes unprecedented dangers.

But besides ever changing socio-environmental influences, what is it in the adolescent biological make-up that predisposes our youth since the beginning of human tradition to challenge theirs and others boundaries? In the last decade through the immense advance of brain imaging technology enabling the in-vivo investigation of neural structures and functional properties, it has become possible to investigate the neural mechanisms underlying adolescent behavioral propensities. This research

has documented unexpectedly large structural and functional maturational transitions in the brain during the second decade of life, in particular in evolutionary young brain areas responsible for the integration of information from the whole brain including brain areas mediating affective states and impulses to guide behavioral output in adaptive ways. Immaturity of this neural system presumably in conjunction with a rise in steroids at the beginning of puberty has been proposed by developmental neuroscientists to be reflected in difficulties in affect regulation. Thus, while adolescents may be very well able to cognitively reflect on the hypothetical consequences of risky actions, they fail (at least more so than adults) to implement this knowledge when faced with a situation in which emotions skyrock such as an intimate encounter with an attractive peer, when faced with a shiny new mobile phone, or when challenged in a dispute with parents about the time at which to be home at night. And when adolescents experience adverse feelings such as sadness, they will have more difficulties than adults to regulate these affective states by means of cognitive strategies.

Now, despite the increasing knowledge and interest in brain maturation during adolescence, little research to date has directly examined the influence of motivationally challenging stimuli on cognitive control in healthy adolescents and adolescents with mood and anxiety disorders employing basic neuroscience measures apart from functional resonance imaging with its known limitations in temporal resolution. The research presented in the current thesis aimed to address this gap by investigating cognitive control in healthy adolescents and adolescents with mood and anxiety disorders using a saccadic eye movement task in which cognitive and motivational task demands were systematically varied. Specifically, subjects had to either look at a target (prosaccade) or away from it (antisaccade), and depending on performance could either win or not win a monetary reward, lose or not lose a monetary punishment, or perform the task without monetary implications. Saccadic eye movements were chosen as a research tool because they are non-invasive, can be integrated in paradigms testing executive cognitive processes, are sensitive to incentive manipulation, and finally provide quantitative and easily measurable information on the temporal characteristics of information processing which can be mapped onto neural circuits well delineated from extensive research in non-human primates.

This thesis is divided into a theoretical part consisting of chapters 1 to 4, and an empirical part consisting of chapter 5 to 7. In chapter 1 the phenomenology of adolescent behavioral propensities and mood and anxiety disorders is presented. In chapter 2, findings about structural and functional brain maturation during adolescence and models trying to link these maturational events with adolescent behavioral propensities will be outlined with the respective research in support of each model. In chapter 3, saccadic eye movements as a research tool will be introduced and findings of their use in adolescence and investigation of reward-related information processing will be presented. Chapter 4 outlines the hypotheses that will be addressed in the second part of this thesis, which starts with the presentation of the experimental procedures in chapter 5 used to address the proposed hypotheses. In chapter 6 and 7, the results concerning cognitive control under incentives in healthy adolescents as compared to adults and as compared to adolescents with major depressive disorder and with an anxiety disorder will be presented and discussed.

II. THEORETICAL BACKGROUND

1. Adolescence – A Time of Storm and Stress

Adolescence refers to the stage of human development in which a child matures into an adult, thereby passing through many physiological, psychological and sociobehavioral transitions. No single event signals the on- and offset of adolescence (Spear, 2000), and thus time margins of the adolescent age range vary from 10 - 14 at its lower end up to 18 - 25 years, depending on culture, gender, and transition at focus. The World Health Organization (WHO) for example defines adolescence as the period of life between 10 and 19 years of age. The NIMH supported interdisciplinary research network ADAPT (Adolescent Development Affect-Regulation and the Pubertal Transition Network) defines adolescence as the time span between sexual maturation (puberty onset) and attainment of adult roles and responsibilities (Dahl, 2004a).

In almost every measurable physical domain, adolescence is a developmental period of strength and resilience. Yet, despite the abundance of resources, the mortality rate almost doubles between childhood and adolescence and the prevalence of emotional disturbances as well as of severe psychiatric disorders such as schizophrenia, mood and anxiety disorders rises substantially (Dahl, 2004). Accordingly, many philosophers, scientists and writers such as Aristotle and Shakespeare (see also Introduction) have referred to adolescence as a life stage of heightened storm and stress. Below, behavioral and affective propensities during adolescence (chapter 1.1) as well as the prevalence and phenomenology of mood (chapter 1.2) and anxiety (chapter 1.3) disorders during adolescence will be addressed.

1.1 Characteristics of normative Adolescence

An important goal of adolescence among many species is to achieve independence from primary caregivers; and many behavioral features characteristic of this age span seem to serve this purpose (Spear, 2000). For example, during *early* and *mid*-adolescence, there is a marked increase in peer-directed social interactions (Csikszentmihalyi, Larson, & Prescott, 1977), a decline in time spent with parents (Larson & Richards, 1991), and an increase in number and intensity of conflicts with parents (Laursen, Coy, & Collins, 1998; Paikoff & Brooks-Gunn, 1991; Smetana, 1989). During *middle* and *late* adolescence, there is a substantial increase in impulsivity and sensation-seeking, with risk behaviors such as substance abuse, reckless driving, unsafe sexual behaviors and rates of crime peaking in prevalence (Arnett, 1992; Moffitt, 1993). In parallel, there is a stark increase in morbidity and in mortality rate of 200% from childhood to adolescence (Dahl, 2004a), with mainly preventable causes such as accidents, homicides and suicides collectively accounting for more than 85% of deaths (Irwin, 1989). Thus, while adolescent behavioral propensities such as stronger orientation towards peers, risk-taking and sensation-seeking might help adolescents to explore new situations, ac-

quire new behaviors and adult reinforcers, they bear substantial risks for long-lasting negative consequences.

At a more subjective level, the pervasive transitions in physical, psychological and social domains during adolescence bear the potential to overwhelm the adolescent and lead to significant stress (Spear, 2000). The relative stressfulness of the adolescent life period is reflected in assessments of affective behavior at this age. For example, the proportion of time experienced as “very happy”, “proud”, “great” or “in control” declines by as much as 50% between preadolescence and adolescence, while reports of depressed mood and negative affect (i.e. feeling “embarrassed”, “awkward”, “lonely”, “nervous”, “ignored”) as well as reports of greater mood extremes (positive and negative) and frequent mood changes increase compared to preadolescents and adults, even in response to the same or similar events (Larson, Moneta, Richards, & Wilson, 2002; Larson & Richards, 1994; see also Whalen, Jamner, Henker, & Delfino, 2001). In addition to this emotional lability, anxiety and self-consciousness appear to peak during adolescence. These seemingly contradictory adolescent propensities – risk-taking and negative mood states – are according to Spear (2000, pg. 429) compatible from an evolutionary standpoint, since “greater anxiety and emotional reactivity in the face of considerable risk-taking could have proved adaptive for our adolescent ancestral predecessors by serving to increase their vigilance to potential predators during the considerable risks of emigrating from natal territories”.

1.2 Major Depression in Youth

In the past two decades, two leading misconceptions on child and adolescent mood disorders, namely that mood disorders are rare before adulthood (Anthony & Scott, 1960) and that they represent a normative and self-limiting aspect of child and adolescent development (Douvan & Adelson, 1966), have been clearly rejected (Kessler, Avenevoli, & Ries, 2001). Beginning with studies in the 1970’s, developmental researchers demonstrated that the diagnosis of Major Depressive Disorder (MDD) can be made reliably in children and adolescents and documented the large prevalence, continuity into adulthood and negative impact of this disease on (future) psychosocial functioning.

1.2.1 Diagnosis and Phenomenology

Depressive disorders in youth are diagnosed with the same diagnostic criteria and thresholds than in adulthood, with the possible exception that children and adolescents are more likely to present with irritability without clear sadness. According to current diagnostic systems such as the DSM-IV, the diagnosis of major depression requires depressed (or in youth irritable) mood and/or loss of interest along with at least five other symptoms such as significant changes in appetite and sleep, psychomotor retardation or agitation, fatigue or loss of energy, feelings of worthlessness or guilt, diminished ability to think, concentrate or indecisiveness, and suicidal ideation (American Psychiatric Association,

1994). The symptoms need to be present nearly every day most of the day for a period of at least two weeks and need to cause significant distress or impairment in functioning.

Empirical studies largely support the similar symptom phenomenology among adolescents and adults (e.g. Carlson & Kashani, 1988; Kovacs et al., 1984; R. E. Roberts, Lewinsohn, & Seeley, 1995; Strober, Green, & Carlson, 1981), but they also point out some age-specific changes in symptom frequency. For example, Carlson and Kashani (1988) found similar rates of depressed mood, diminished concentration, insomnia and suicidal ideation between preschool children (age 2.5-6), prepubertal children (mean age 9.6 years), adolescents (mean age 14.7 years) and adults (mean age 45.9 years) diagnosed with MDD. In contrast, anhedonia, diurnal variation, hopelessness, psychomotor retardation, and delusions increased with age; and depressed appearance, low self-esteem, and somatic complaints decreased with age.

1.2.2 Prevalence

While the diagnosis of MDD is rare before age 13 (e.g. Costello, Mustillo, Erkanli, Keeler, & Angold, 2003; Kessler et al., 2001; Lewinsohn, Rohde, Klein, & Seeley, 1999; Oldehinkel et al., 1999), it occurs in older adolescents at levels comparable with those in adults. Point prevalence rates based on diagnostic interviews generally range between 1% (McGee & Williams, 1988) and 6% (Kessler & Walters, 1998) and lifetime prevalence between 4% (Whitaker et al., 1990) and 24% (Lewinsohn, Rohde, & Seeley, 1998) by the end of adolescence (for review see Kessler et al., 2001; Zalsman, Brent, & Weersing, 2006). For example, in a representative, prospective community-based study on incidence, prevalence and outcome of depressive disorders in a sample of 1228 German adolescents, Oldehinkel et al. (1999) found a lifetime prevalence for MDD of 5.4% for males and 8.0% for females aged 14-17, steeply increasing to 9.1% in males and 15.4% in females at follow up 20 months later (see Figure 1-1). This gender difference in prevalence with females being stronger affected than males emerged after puberty onset and increased with age, a finding largely supported by other studies (e.g. Costello et al., 2003; Lewinsohn et al., 1999).

The overall variation in prevalence rates among different studies is likely to be due to differences in assessment (e.g. choice of diagnostic interview), sampling (e.g. clinical or community-based sample, age of probands), design (e.g. prospective – retrospective), and to the time the study was conducted with respect to change in diagnostic criteria and impairment thresholds from DSM-III to DSM-IV (Kovacs & Gatsonis, 1994; Oldehinkel et al., 1999). Similar fluctuations have been observed in estimates for lifetime prevalence of MDD in adults ranging from 4.4% to 18.0% (Bland, 1997; Wittchen, Knauper, & Kessler, 1994). Of note, there is growing evidence not only for an earlier onset of depression but also a general increase in prevalence in cohorts born after World War II (Bland, 1997; Cross-National Collaborative Group, 1992).

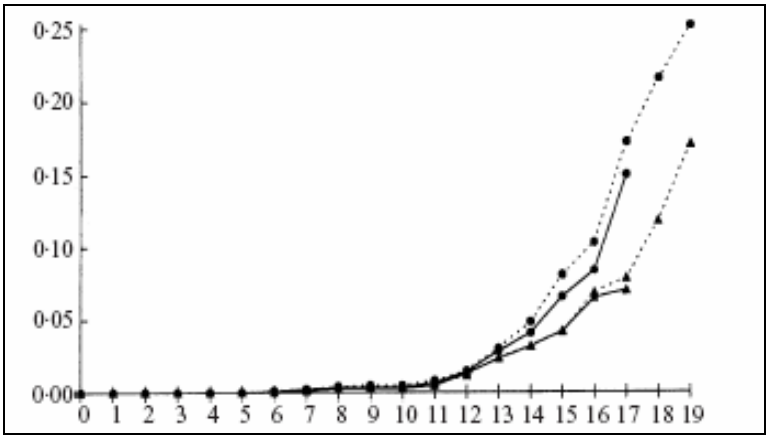

Figure 1-1: Age of onset curves (cumulative hazards by means of Kaplan-Meyer estimates) of major depressive disorder, by gender (▲ male; ● female), baseline (—) and follow-up (….) estimates. Adapted from Oldehinkel et al. (1999).

1.2.3 Comorbidity

Adolescents with MDD frequently present with comorbid psychiatric disorders, especially with anxiety disorders, disruptive behavior disorders such as oppositional defiant disorder, and substance abuse disorder. Costello, Mustillo, Erkanli, Keeler, and Angold (2003) for example demonstrated in a sample of 9-16 year old adolescents significant concurrent comorbidity (i.e. the co-occurrence of 2 or more diagnoses at the time of measurement) between any depressive disorder and any anxiety disorder (OR = 28.9), Oppositional Defiant Disorder (OR = 16.7), and Substance Abuse Disorder (OR = 10.4). According to Kessler et al. (2001) up to three fourths of depressed adolescents have a history of at least one anxiety disorder. Frequently, the anxiety disorder antecedents the depressive disorder (Pine, Cohen, & Brook, 2001; Zalsman et al., 2006), however, it is unclear if presence of an anxiety disorder is a risk factor or a risk marker of depression, or if it arises due to some shared risk factors that are common to both conditions (Kessler et al., 2001).

1.2.4 Course and outcome

Longitudinal studies in clinical (e.g. Harrington, Fudge, Rutter, Pickles, & Hill, 1990; Kovacs et al., 1984; Rao et al., 1995; Weissman et al., 1999) as well as community settings (e.g. Lewinsohn et al., 1999; Pine, Cohen, Gurley, Brook, & Ma, 1998) suggest a high recurrence rate, continuity and specificity of adolescent-onset MDD into adulthood and outline its negative impact on psychosocial functioning.

In terms of *recurrence*, longitudinal studies document that 70% of adolescents with MDD experience another depressive episode until young adulthood, a rate comparable to the recurrence rate of adults with unipolar depression (Coryell et al., 1989). Overall, rates seem higher in clinical as compared to community-based samples. For example, in clinically referred samples, Kovacs et al. (1984) found a recurrence rate of 72% within five years in 41 adolescents with MDD with or without comorbid

dysthymia, and Rao et al. (1995) found a recurrence rate of 69.2% in 26 adolescents with MDD at follow-up seven years later (see Figure 1-2). In a community-based prospective study Lewinsohn et al. (1999) reported that 45% of 238 subjects with adolescent MDD relapsed between age 19 and age 24. Pine et al. (1998) found that 23 adolescents with MDD with a mean age of 13.7 years from a community survey had a 4-fold increased risk of MDD until age 22 (OR = 4.36, 95% CI = 1.65-11.57). Finally, 40% of adults with MDD retrospectively report to have had onset of the disease before age 20 (Bland, 1997).

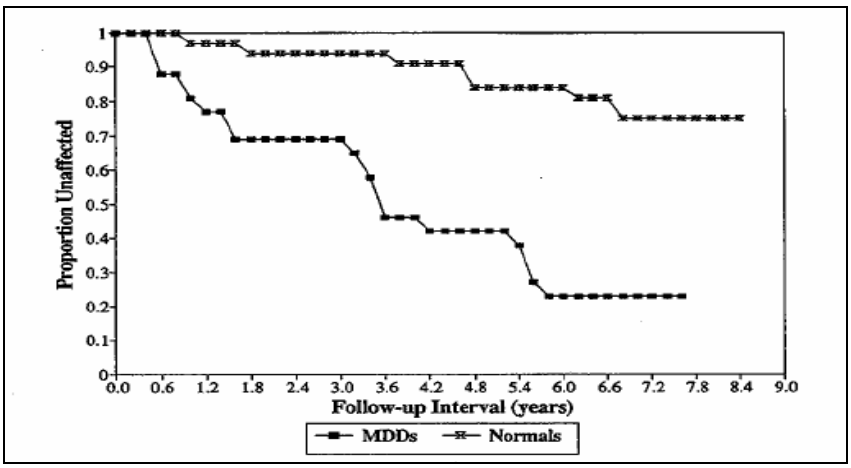

Figure 1-2: Survival from depression during follow-up interval in the subjects with MDD at initial assessment (mean age 15.4 years) and normal controls. From Rao et al. (1995).

In terms of *specificity*, several studies document that adolescents with MDD have an increased risk for every type of affective disorder in adulthood. For example, in the above mentioned study by Rao et al. (1995), adolescent-onset MDD subjects had compared to matched controls an increased risk for developing MDD (69.2% vs. 18.2%), but also dysthymia (26.9% vs. 0%) and bipolar disorder (19.2% vs. 0%). Costello et al. (2003) found an increased risk for developing an anxiety disorder by age 16 for girls with any depressive disorder. However, adolescents with MDD do not have a higher risk for other psychiatric disorders in adulthood, unless they presented already in adolescence with a comorbid non-depressive disorder (e.g. Harrington et al., 1990; Lewinsohn et al., 1999; Weissman et al., 1999).

In terms of *outcome*, adolescent-onset MDD has great negative impact on social development and life course role transitions (Kessler et al., 2001). For example, adolescents with recurrent MDD compared to adolescents with only one episode of MDD and compared with non-affected individuals achieve lower educational status, have increased rates of psychiatric and medical hospitalizations, exert more risky behaviors such as smoking, drinking or bingeing and become earlier parents than non-affected individuals (e.g. Glied & Pine, 2002; Harrington et al., 1990; Lewinsohn, Rohde, Seeley, Klein, & Gotlib, 2000; Oldehinkel et al., 1999; Rao et al., 1995; Weissman et al., 1999). These associations also persist when controlling for low socioeconomic status, which is a risk factor for both, adoles-

cent-onset MDD and risky behaviors such as drinking or smoking (Glied & Pine, 2002; Rao et al., 1995). In addition, many of the negative consequences of adolescent depression such as teenage pregnancy or low educational achievement result in low socioeconomic status and themselves increase the risk for recurring with depression. Not surprisingly, clinical depression is currently the leading cause of disability in many industrialized countries, and according to the World Health Organization is expected to become the second leading cause of disability worldwide (after heart disease) by the year 2020 (Murray & Lopez, 1997). The most serious consequences of depressive disorders are suicidal ideation and behavior. Depression is the strongest psychiatric correlate of suicide and suicide attempts in the adolescent age group (Brent et al., 1993; Foley, Goldston, Costello, & Angold, 2006). For example, in the study of Weissman et al. (1999), 7.7% of 91 subjects with adolescent-onset MDD committed suicide, 50.6% of 73 of these subjects made a suicide attempt, and 23% multiple suicide attempts over their lifetime until follow-up at age 26. Compared with the healthy control group, subjects with adolescent-onset MDD had a more than 14-fold increased risk for a first suicide attempt over their lifetime until follow-up at age 26 years.

1.2.5 Risk factors for o- and recurrence

Genetic and adverse environmental factors and their interactions – from a background of profound maturational changes in brain structure and function as reviewed in chapter 2 - increase the risk for developing depression in adolescence. The strongest predictors for the emergence of child and adolescent depression is parental psychopathology (e.g. parent suffering from depression) and low socioeconomic status with some of its correlates such as family violence, neglect, sexual abuse, parent loss, growing up in a single-parent household (for review see Kessler et al., 2001; Zalsman et al., 2006). For example, in a study by Glied and Pine (2002), almost one fourth of girls with history of either physical or sexual abuse met criteria for depression, and adolescents who had experienced severe life stresses in the year before the assessment were much more likely to meet criteria for depression than were those whose lives had been less stressful. However, some of these predictors are not only predicting subsequent depression, but a wide range of common mental disorders (Kessler, 1997). In general, childhood onset MDD seems to be the response to a chaotic environment and is less closely associated with recurrence than adolescent-onset MDD, which has a greater genetic component (Scourfield et al., 2003).

In light of the high negative impact of recurrent adolescent MDD on psychosocial functioning, several researchers attempted to find factors that predispose affected individuals for recurrence of the disorder (Kovacs et al., 1984; Lewinsohn et al., 2000; Rao et al., 1995). So far, the results of these studies are inconsistent. In sum, there is some evidence for an association between risk for recurrence and low socioeconomic background, comorbidity with dysthymia, presence of Borderline personality disorder symptoms, previous history of recurrence and a family history of (recurrent) MDD.

1.3 Anxiety Disorders in Youth

In contrast to research on MDD, there is little research on childhood and adolescent anxiety disorders, and findings from this research have been inconsistent (Pine, 1997). Reasons are uncertainty regarding boundaries for the various anxiety disorders, difficulties in defining impairment thresholds and lack of instruments measuring distinct childhood anxiety disorders with acceptable psychometric properties (Greenhill, Pine, March, Birmaher, & Riddle, 1998).

1.3.1 Diagnosis

There are 10 clinical anxiety disorders that affect children as defined in the DSM-IV (American Psychiatric Association, 1994): Panic disorder with or without agoraphobia (PD), agoraphobia without panic disorder (AgP), specific phobia (SpP), social phobia (SoP), obsessive-compulsive disorder (OCD), post-traumatic stress-disorder (PTSD), acute stress disorder, generalized anxiety disorder (GAD), and separation anxiety disorder (SAD). Of note, the DSM-III-R Overanxious Disorder (OAD) has been subsumed in DSM-IV under Generalized Anxiety Disorder.

There are several difficulties in reliably diagnosing an anxiety disorder in youth. For example, since anxiety is a normative and adaptive emotion linked to specific developmental stages, the distinction between “normal” and “clinical” anxiety is not always straightforward. Separation anxiety disorder for example resembles the normal phase of separation anxiety in toddlers (R. G. Klein, 1995), and some phobias resemble developmentally appropriate phases of shyness, fears of the dark, or small animals (Marks, 1987). Therefore, for reliably diagnosing an anxiety disorder, a significant impairment in functioning and distress is required, and the anxiety should be inappropriate for the actual developmental stage of the child (i.e. separation anxiety in a 10-year old) (Pine, 1997). Further complicating diagnosis is the extensive symptom overlap among the different anxiety disorders as well as between some anxiety and depressive disorders (Costello, Egger, & Angold, 2005; Labellarte, Ginsburg, Walkup, & Riddle, 1999). For example, school refusal may be an anxiety-related symptom associated with separation anxiety disorder, social phobia, generalized anxiety disorder or major depression (Last & Strauss, 1990). Finally, because children can only provide limited valid information about anxiety, the diagnosis of childhood anxiety requires assessment and integration of symptoms from both, parents and children (Pine, 1997).

1.3.2 Prevalence

In an extensive review of all published epidemiologic studies between 1993 and 2004 on prevalence of anxiety disorders in children and adolescents aged 4 - 21 years employing DSM-III-R or DSM-IV, Costello et al. (2005) report 6-month prevalence estimates between 5.5% and 17.7%, and lifetime estimates between 8.3% and 27.0%. Particularly high prevalence estimates are reported for OAD with a 6-month prevalence rate between 1.9% and 7.1%; social phobia with a 6-month preva-

lence rate between 2.0% and 9.2%, and specific phobias with a 6-month prevalence rate between 2.6% and 12.9%. Panic disorder, GAD and OCD in contrast are infrequent in youth (Merikangas, 2005). Thus, anxiety disorders are among the most prevalent conditions afflicting children, however, prevalence rates vary substantially, presumably due to varying impairment thresholds employed (Costello et al., 2005; Pine et al., 1998; Wittchen & Fehm, 2003).

Just as stranger anxiety and separation anxiety symptoms emerge during specific stages of normal development, anxiety disorders also have different peak onset times. For example, the median age at onset for specific phobias and separation anxiety disorder is age 7, followed by social phobia at age 13, OCD at age 19, agoraphobia at age 20, PTSD at age 23, panic disorder at age 24 and GAD with a median onset age of 31 years (Kessler et al., 2005) (see also Figure 1-3). Across all developmental stages and all subtypes of anxiety disorder, the prevalence is higher in girls than in boys (for review see Merikangas, 2005).

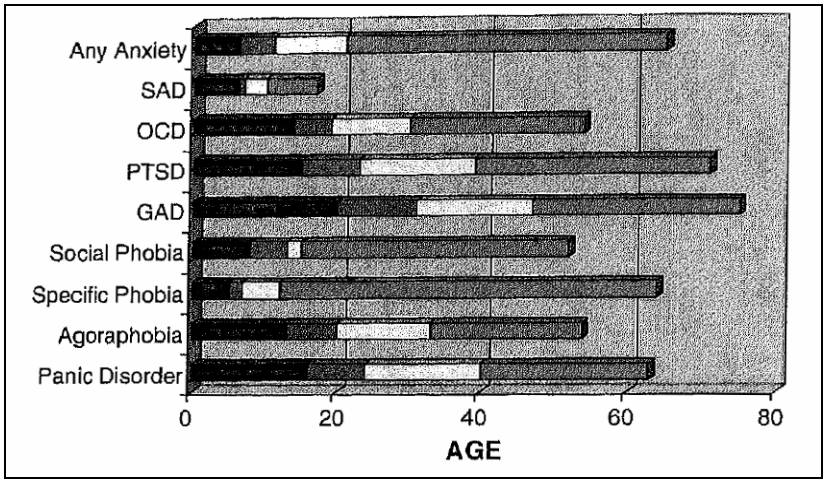

Figure 1-3: Median age at onset of anxiety disorders in the United States general population (N = 9282). Black, 25th percentile, dark grey, 50th percentile; white, 75th percentile, light grey, 99th percentile. From Merikangas (2005). SAD: Separation Anxiety Disorder; OCD: Obsessive Compulsive Disorder; PTSD: Posttraumatic Stress Disorder; GAD: Generalized Anxiety Disorder.

1.3.3 Comorbidity

Among anxiety disorders, only phobias (i.e. specific, social and agoraphobia) are highly comorbid with each other (Costello et al., 2005). In addition, there is large comorbidity between anxiety disorders and depression. For example, a review of available studies on comorbidity published 1999 by Angold, Costello, and Erkanli (1999) showed that, controlling for other comorbid disorders, children with anxiety disorders were 8.2 times more likely to suffer from depression than controls (OR = 8.2), and 3 times more likely to suffer from a comorbid behavioral disorder (OR for conduct disorder = 3.1, OR for ADHD = 3.0). Costello et al. (2003) found significant concurrent comorbidity in a sample of 9-16 year old adolescents between any anxiety disorder and any depressive disorder (OR = 27.9) or ADHD (OR = 3.4).

1.3.4 Course and outcome

There is evidence for *continuity* into adulthood, i.e. children and adolescents with anxiety disorders have an increased risk to have an anxiety disorder also in adulthood. Pine (Pine, 1999; Pine et al., 1998) for example reported in a prospective epidemiological study that adolescents with a history of social phobia, generalized anxiety disorder or major depression face a 45% chance of suffering from these disorders six years later compared to 5% in healthy controls. These data are consistent with retrospective reports of adults with anxiety disorders suggesting that the onset of anxiety disorders generally occurs in childhood or adolescence (Merikangas, 2005; Otto et al., 2001).

In terms of *specificity*, there is evidence for a high homotypic continuity of all anxiety disorders except for specific phobias (Costello et al., 2003). In terms of heterotypic continuity, there is evidence that separation anxiety disorder predicts panic disorder and agoraphobia (Gittelman & Klein, 1984; but see Otto et al., 2001). Moreover, in a study by Bittner et al. (2004), all adolescents with comorbid anxiety disorders and anxiety disorders characterized by severe impairment were at increased risk for later developing MDD.

In terms of *impairment*, some studies document a high degree of internal stress engendered by childhood anxiety disorders (Benjamin, Costello, & Warren, 1990; Ialongo, Edelsohn, Werthamer-Larsson, Crockett, & Kellam, 1995). Moreover, early onset of anxiety disorders is associated with greater severity and with comorbidity of the disorder with depression in adults (Otto et al., 2001). In addition, anxiety disorders affect functioning by complicating the expression of other comorbid disorders. For example, when comorbid with depression, anxiety disorders substantially increase the risk for suicide (Foley et al., 2006), and when comorbid with ADHD may be less responsive to psychostimulant medication (Tannock, Ickowicz, & Schachar, 1995). In an epidemiologic study by Ezpeleta, Keeler, Erkanli, Costello, and Angold (2001), anxiety disorders were as likely to result in disability as depressive disorders also when controlling for comorbidity with other psychiatric disorders. However, level of impairment depends on the type of anxiety disorder; for example, OCD and social phobia are more impairing than specific phobias.

1.3.5 Risk factors for developing an anxiety disorder in youth

As reviewed by Merikangas (2005) and Pine (1997) several behavioral and physiological risk factors for developing an anxiety disorder have been identified, such as behavioral inhibition (i.e. increased physiologic reactivity and behavioral withdrawal in face of novel or challenging situations), increased anxiety sensitivity (i.e. belief that anxiety sensations are dangerous), increased vigilance to threat cues and stressful stimuli (see also chapter 2.2.3.1.3), enhanced autonomic reactivity, poor immune system, enhanced respiratory sensitivity, and various neurobiologic and neuroendocrine factors. Environmental risk factor for developing an anxiety disorder are infections and especially high fever during the first year of life, head injury, overprotective, less caring or anxious parents, low socioeconomic status, severe childhood traumas (required for diagnosis of PTSD). As with depression, a

major risk factor for developing an anxiety disorder is parent psychopathology. Family studies for example indicate a three-to fivefold increased risk of anxiety disorders among first-degree relatives of affected subjects compared with controls, twin-studies indicate higher rates of anxiety disorder for monozygotic compared with dizygotic twins, and high-risk studies show on average a 3.5-fold increased risk for developing an anxiety disorder in children from parents with an anxiety disorder compared with offspring from controls. However, offspring of parents with an anxiety disorder also face an increased risk for developing depression compared to offspring from controls. Moreover, linkage studies failed to identify specific genes conferring increased risk of anxiety disorder. Therefore, most theories assume a broader underlying genetic predisposition for the development of anxiety and other psychiatric expressions such as persistent worrying or depression, depending on internal and environmental factors affecting brain maturation (R. J. Davidson, 1998; Grillon, Dierker, & Merikangas, 1997).

1.4 Synopsis chapter 1

Adolescence is a time of “storm and stress”, characterized by three central features of turmoil: mood disruptions, risk behaviors, and conflict with parents (Arnett, 1999). In addition, there is a marked increase in prevalence of mood and anxiety disorders during adolescence. However, contrary to earlier conceptions, adolescent mood and anxiety disorders are not just extreme reflections of the general and transient emotional turmoil experienced by adolescents during the passage through this challenging developmental age span. In contrast, early-onset mood and anxiety disorders exhibit all clinical features of adult mood and anxiety disorders, represent a major risk factor for suffering from recurrent severe episodes of illness in adulthood, and through their presence at a time where the course is set for later psychosocial functioning may have severe implications for later academic and social achievement.

2. Developmental Cognitive Neuroscience

With the great technological and methodological advances in the neurosciences within the past two decades it has increasingly become possible to investigate structural and functional brain maturation in pediatric populations and its influence on behavior and cognition (for review see Munakata, Casey, & Diamond, 2004; Paus, 2005). Evidence from this new scientific approach, also referred to as developmental cognitive neuroscience, suggests that adolescent behavioral propensities such as impulsivity and emotional turmoil in part result from the ongoing maturation of brain circuits underlying the cognitive and affective control of behavior (Giedd, 2004; Luna & Sweeney, 2004). Moreover, these maturational transitions in brain organization have been proposed to increase the vulnerability for developing a psychiatric disorder such as substance abuse, schizophrenia, or mood and anxiety disorders (Pechmann, Levine, Loughlin, & Frances, 2005; Steinberg, 2005), conditions rising substantially in prevalence at this age. Thus, understanding neurodevelopment during the adolescent period may not only help understand adolescent behavior, but may also contribute to our understanding of the pathophysiology of severe psychiatric disorders (Luna & Sweeney, 2004). Below, the structural, functional, and hormonal processes underlying brain maturation during adolescence will be addressed (see chapter 2.1). Subsequently, different developmental cognitive neuroscience models on specific adolescent behavioral propensities, impulsivity and negative mood states such as anhedonia and anxiety, will be outlined in more detail (see chapter 2.2).

2.1 Brain development during Adolescence

The conventional view of structural brain maturation has been that most of it occurs in utero and is concluded by middle-to-late childhood. First insights indicating maturational changes in the brain beyond childhood emerged in the late 1960's and 1970's with post-mortem examinations of adolescent brains (Huttenlocher, 1979; Yakovlev & Lecours, 1967). This knowledge was further advanced in the 1990's with the advent of structural and functional imaging methods, enabling developmental neuroscientists to investigate structural and functional maturation of the brain non-invasively and in vivo in pediatric populations. Today, it is well established that the adolescent brain is a brain in flux, undergoing numerous pro- and regressive changes, resulting in a highly efficient multimodal processing system by early adulthood.

2.1.1 Structural brain maturation

In terms of size, weight, folding and regional functional specialization the brain is largely in its adult form by early childhood (Casey, Galvan, & Hare, 2005; Giedd, 2004). Subsequent maturational changes are structurally more subtle, but nonetheless crucial in terms of their functional significance. Most striking are a steady increase in white matter volume, and an initial increase followed by a subsequent decrease in gray matter throughout the cortex and related subcortical structures such as the basal ganglia, amygdala and hippocampus (for review see Blakemore & Choudhury, 2006; Casey, Tottenham et al., 2005; Giedd, 2004; Paus, 2005) (see Figure 2-1).

The increase in white matter results from the progressing isolation of neuronal fibers with myelin, a phospolipid layer which appears white on fresh brain sections. Myelin acts as an insulator and leads to increased speed (up to 100 fold) of electrical signals between neurons. The increase in gray matter results from the continuous dendritic arborization of neurons and the growth of synapses (i.e. connection points) between them. The subsequent loss of gray matter may be due to intra-cortical myelination and/or to the elimination (so-called pruning) of redundant synapses (Blakemore & Choudhury, 2006; Paus, 2005). Synaptic pruning has been proposed to be experience-dependent, i.e. only active synaptic connections survive, while unused ones die. The functional significance of experience-dependant synaptic pruning is according to Luna and Sweeney (2004) to enhance the computational capacity of local neural circuits and according to Casey et al. (2005) to sculpt the brain on the basis of experience to effectively accommodate to environmental needs. Parallel to synaptogenesis and synaptic pruning, there is an increase followed by a decline in brain activity between childhood and adolescence as indexed for example by measurement of glucose metabolism (Chugani, 1998; Chugani, Phelps, & Mazziotta, 1987).

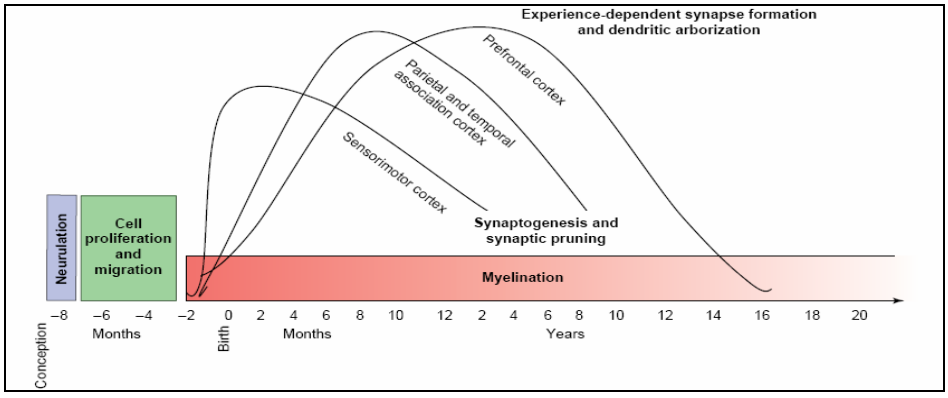

Figure 2-1: Developmental course of human brain development. Proliferation and migration of neurons largely occurs during fetal development, regional changes in synaptic density occur during postnatal development following a U-shaped developmental course, and myelination lasts well into adulthood. From Casey et al. (2005).

On a regional level, there are important differences in course and timing of white and gray matter maturation. For example, while white matter volume increases linearly until adulthood with similar slope of increase in the four major lobes of the brain (frontal, parietal, temporal, occipital), gray matter not only follows an inverted U-shape developmental course but also exhibits large regional variations in extent and time course (see Figure 2-1). In general, evolutionarily older regions associated with more basic functions such as the sensorimotor cortices mature before evolutionarily younger regions involved in more complex and integrative tasks such as the higher order association cortices (Gogtay et al., 2004). One of the last regions to mature is the prefrontal cortex (PFC), reaching adult dimensions not before the early 20's (Giedd, 2004; Giedd et al., 2006). Subcortically, changes in gray matter are observed in the forebrain, in particular the basal ganglia, a structure that is highly interconnected with the PFC (Giedd et al., 2006; Sowell, Thompson, Holmes, Jernigan, & Toga, 1999), in the amygdala in males and in the hippocampus in females (Giedd et al., 1996) (see Figure 2-2).

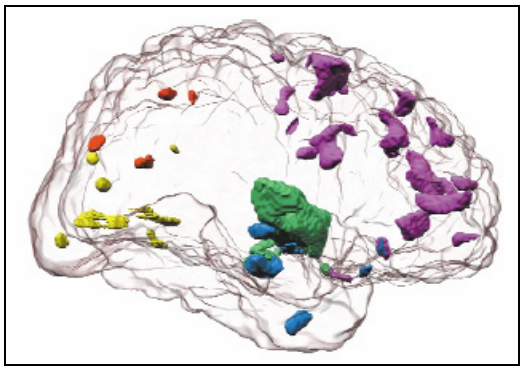

Figure 2-2: Three-dimensional picture of gray matter density reductions observed between adolescents (mean age 13.8 years) and adults (mean age 25.6 years). Clusters are color-coded based on location: Frontal lobes (purple), parietal lobe (red), occipital lobe (yellow), temporal lobe (blue), subcortical (green). From Sowell et al. (1999).

2.1.2 Functional brain maturation

Concurrent with structural brain maturation, adolescents show continuous improvements in cognitive abilities underlying the cognitive or executive control of behavior such as working memory (the ability to maintain and manipulate information online), selective attention (the ability to ignore irrelevant and focus on relevant information), inhibitory control (the ability to inhibit context inappropriate but prepotent response tendencies), cognitive flexibility (i.e. shifting attention between rules), and strategic planning (e.g. Bunge, Dudukovic, Thomason, Vaidya, & Gabrieli, 2002; Carver, Livesey, & Charles, 2001; Cepeda, Kramer, & Gonzalez de Sather, 2001; Crone, Ridderinkhof, Worm, Somsen, & van der Molen, 2004; De Luca et al., 2003; Durston et al., 2002; Fischer, Biscaldi et al., 1997; Gathercole, Pickering, Ambridge, & Wearing, 2004; Huizinga, Dolan, & van der Molen, 2006; Leon-Carrion, Garcia-Orza, & Perez-Santamaria, 2004; Luciana, Conklin, Hooper, & Yarger, 2005; Luna & Sweeney, 2004; B. R. Williams, Ponesse, Schachar, Logan, & Tannock, 1999)

Functional magnetic resonance imaging (fMRI) studies, investigating the neural activity during performance of such higher order cognitive functions, indicate that these improvements are paralleled by the continuous integration of neural networks orchestrated by the PFC. For example, while children and young adolescents show diffuse patterns of brain activation in task-specific (i.e. activity is correlated with task-performance) as well as task-irrelevant (activity is not correlated with task-performance) cortical and subcortical brain areas, older adolescents and adults recruit only focal, task-specific brain areas (e.g. Adleman et al., 2002; Bunge et al., 2002; Crone, Wendelken, Donohue, van Leijenhorst, & Bunge, 2006; Durston et al., 2002; Klingberg, Forssberg, & Westerberg, 2002; Kwon, Reiss, & Menon, 2002; Luna et al., 2001; Rubia et al., 2000; Rubia et al., 2006; Tamm, Menon, & Reiss, 2002). Moreover, with increasing age, there is an increase in activity in task-specific prefrontal areas during performance of cognitive functions (Casey, Tottenham et al., 2005) (see Figure 2-3), and a decrease of activity in subcortical regions (Casey et al., 2004; Casey, Thomas, Davidson, Kunz, & Franzen, 2002; Luna et al., 2001; Monk, McClure et al., 2003; Thomas et al., 2004).

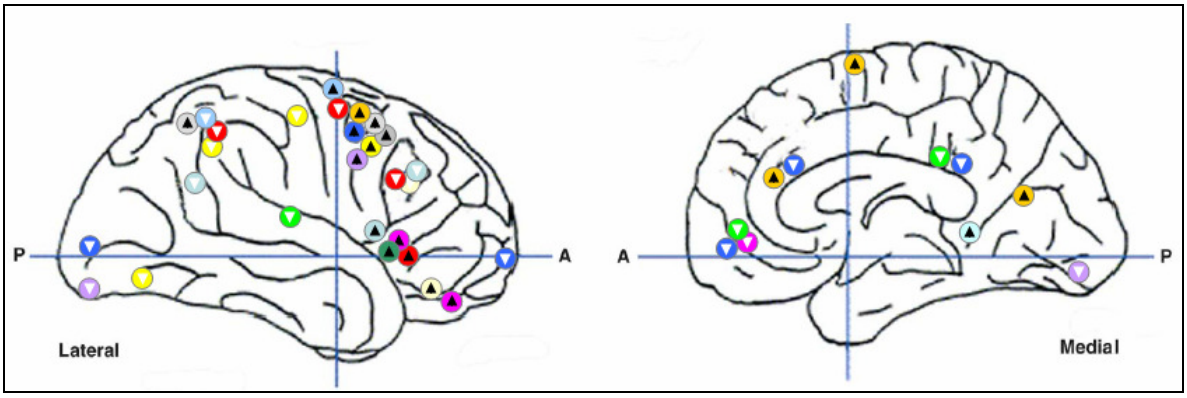

Figure 2-3: Collectively, developmental neuroimaging studies of cognitive control processes suggest a general pattern of increased recruitment of slow maturing prefrontal cortex, especially dorsolateral and ventral prefrontal cortex, and decreased activation of lower level sensory regions, including extrastriate and fusiform cortex and posterior parietal cortex areas. Of note, activations vary with task demands, for example working memory tasks recruit different areas (within PFC and within overall neocortex) from response inhibition tasks. This pattern of activity suggests that higher cognitive abilities supported by association cortex become more focal and fine-tuned with development, whereas other regions not specifically correlated with that specific cognitive ability become attenuated. ▲ = Increasing activation with age; ▼= Decreasing activation with age; colors correspond to single studies, A = anterior, P = posterior. Adapted from Casey et al. (2005).

The exact neural processes mediating the cognitive improvements during adolescence cannot be determined with the current spatial resolution of fMRI, however, it seems likely that they result from the fine-tuning and myelination of neural projections within the PFC and/or between the PFC and its cortical and subcortical projections sites - setting the stage for decreased susceptibility to interference of signal transmission (Nagy, Westerberg, & Klingberg, 2004) and increased PFC “top-down” control of behavior (Luna & Sweeney, 2004). In support for this hypothesis, in two studies employing diffusion tensor imaging (DTI), a relatively new MR technique revealing microstructural properties of white matter (Watts, Liston, Niogi, & Ulug, 2003), working memory capacity during development was positively correlated with prefrontal-parietal connectivity (Nagy et al., 2004; Olesen, Nagy, Westerberg, & Klingberg, 2003) and inhibitory control with fronto-striatal connectivity (Liston et al., 2006).

2.1.3 Puberty and brain maturation

Puberty refers to the re-activation of the hypothalamic-pituitary-gonadal (HPG) axis at the end of childhood that initiates gonadarche (i.e. growth of ovaries in girls and testes in boys and an up to 26-fold increase in production of sex steroids such as testosterone and estradiol (Ducharme & Forest, 1993)) and culminates in gonadal maturation and expression of secondary sexual characteristics (for review see Buchanan, Eccles, & Becker, 1992; Cameron, 2004; Dahl, 2004a; Sisk & Foster, 2004). The process begins in girls approximately at age 8, in boys at age 10 (Strauch, 2004). Other hormonal changes occurring at around puberty are an increase in androgen secretion by activation of the hypothalamus-pituitary-adrenal (HPA) axis (adrenarche) and an increase in hormones controlling body growth.

In most mammals, the HPG axis is transiently active already during late prenatal and/or early postnatal life. Traditionally, it was believed that this first short peak in gonadal steroid production serves the sexual differentiation of neural circuits involved in reproductive behavior (so-called organizational effects of steroids), and that the pubertal re-awakening of the HPG-axis and gonadal steroid production serves the activation of those circuits (so-called activational effects of steroids) (for review see Arnold & Breedlove, 1985; Romeo, 2003; Sisk & Foster, 2004). However, recent evidence suggests that gonadal steroids may organize neural circuits also during puberty (for review see Giedd et al., 2006; Romeo, 2003; Schulz & Sisk, 2006; Sisk & Foster, 2004) (see Figure 2-4). For example, rodents exhibit adult steroid-sensitive behaviors such as mating or territorial scent marking appropriately only if they were exposed to steroids during puberty.

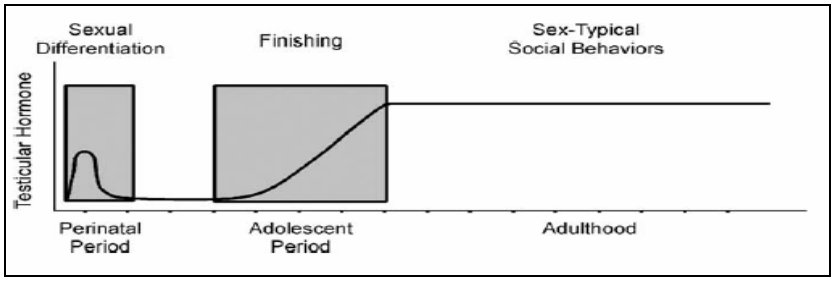

Figure 2-4: Two stage model of the development of sex-typical social behaviors proposed by Schulz and Sisk (2006): Perinatal hormone secretions sexually differentiate behavioral neural circuits and pubertal hormone secretions refine and "finish" these processes during adolescence to allow for the display of sex-typic social behaviors in adulthood.

In addition, the organizational effects of hormones may not only afflict on brain regions involved in sexual performance, but on a wide network of brain regions that mediate the sensory, motor, and affective responses enabling sexual behavior (Becker, 1999; Cameron, 2004; Sisk & Foster, 2004) (see Figure 2-5). For example, receptors for steroids have been found in several limbic brain regions such as the amygdala, lateral septum, bed nucleus of the stria terminalis, and Nucleus accumbens (for references see Cameron, 2004; Stevens, 2002) (see Figure 2-6). The limbic system has been attributed an important role in mediating affective states in the brain (see also chapter 2.2.2).

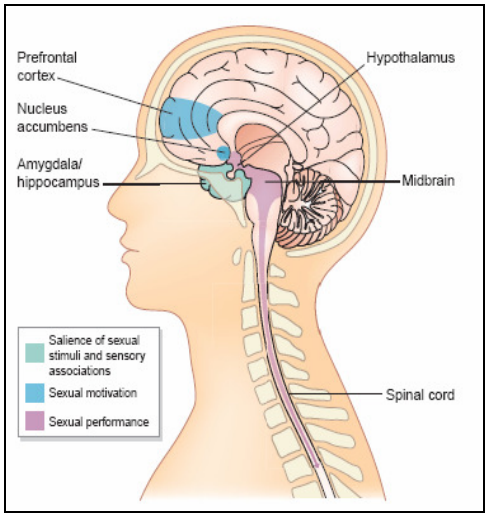

Figure 2-5: Reproductive behavior requires neural circuits involved in salience of sexual stimuli and sensory association, sexual motivation and sexual performance. From Sisk and Foster (2004).

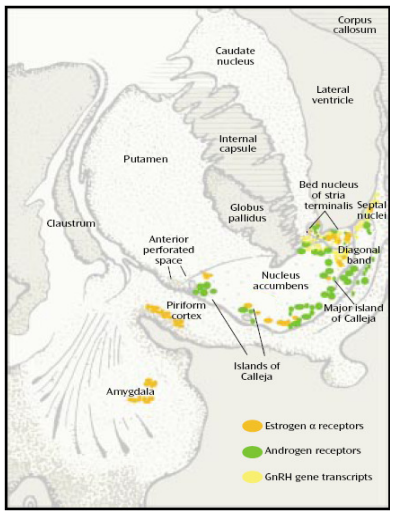

Figure 2-6: Receptors for gonadal steroids in basal forebrain sites. From Stevens (2002).

The immense surge of steroids at puberty with their influence on many brain areas raises the question about their effect on adolescent behavioral propensities. Indeed, while cognitive development seems to proceed independently of hormonal maturation as evident from case studies of adolescents with delayed or premature puberty (for review see Dahl, 2004a), some studies do document associations between pubertal developmental stage and some affective measures such as increases in sexual motivation, romantic interest, emotional intensity, sensation seeking and risk-taking behavior (Dahl, 2004a; Martin et al., 2002; Steinberg, 2005). Yet to date there is inconsistent evidence causally linking levels of specific hormones to adolescent behavioral propensities, suggesting that other bio-psycho-social factors such as state of brain maturation, environmental stress, genetic predisposition, or interactions between different hormones may mediate the influence of steroids on adolescent behavior (for review see Buchanan et al., 1992; Spear, 2000; Walker, Sabuwalla, & Huot, 2004).

2.2 Neuroscience models of adolescent behavioral propensities: Starting the engines with an unskilled driver?

The different time courses along which the specific brain systems during adolescence mature have provided the backbone against most developmental neuroscience models of adolescent emotional and behavioral propensities have been placed (e.g. Chambers & Potenza, 2003; Chambers et al., 2003; Dahl, 2004a; Ernst et al., 2006; Luna & Sweeney, 2004; Nelson, Leibenluft, McClure, & Pine, 2005; Spear, 2000; Steinberg, 2004). Specifically, these models suggest that the slow, age and experience-dependant maturation of the PFC during adolescence results in diminished regulatory cognitive control over earlier maturing, puberty-sensitive brain circuits mediating affective states and arousal, biasing adolescent behavior towards more impulsive, affect-steered patterns (see Figure 2-7). Accordingly, Ronald Dahl from the NIMH interdisciplinary research network ADAPT (Adolescent Development Affect-Regulation and the Pubertal Transition Network) has compared adolescence to "starting the engines with an unskilled driver" (Dahl, 2004b, pg. 17).

Thus, form a developmental neuroscience perspective, an important challenge of adolescence is the functional integration of brain structures mediating regulatory cognitive control with those mediating affect and arousal (Luna & Sweeney, 2004). Behaviorally, the successful passage through this "critical or sensitive period for a reorganization of regulatory systems" (Steinberg, 2005, pg. 69) is paralleled by the increasing use of effective impulse control and emotion regulation skills, enabling the adolescent to navigate and control his or her impulses and emotions in service to long-term adaptive goals (Dahl, 2003, 2004a).

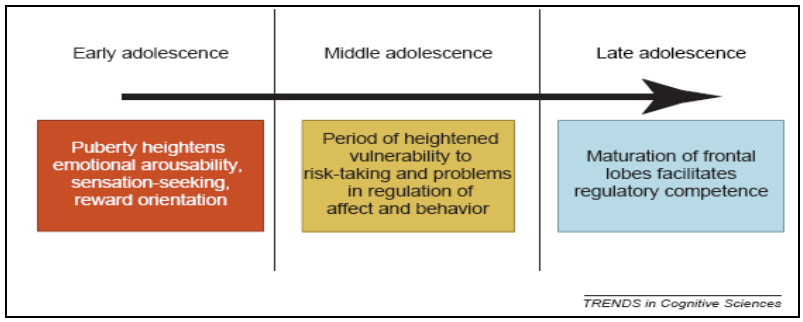

Figure 2-7: Neural models of adolescent behavior suggest that the impact of puberty on arousal and motivation occurs before maturation of the frontal lobes is complete. This gap may create a period of vulnerability to problems in the regulation of affect and behavior. From Steinberg (2005).

In this section, first neuroscience-based models on the neural mechanisms underlying affect, and its regulation, will be outlined in more detail (chapter 2.2.1). Subsequently, two adolescent propensities which have been proposed to result from the maturational disjunction between developing brain, regulatory and behavioral/affective systems will be addressed from a developmental cognitive neuroscience perspective: Impulsive behaviors such as risk-taking (chapter 2.2.2), and increase in negative affective states such as anhedonia, depressed mood and anxiety (chapter 2.2.3).

2.2.1 Affect and its regulation in Cognitive Neuroscience

At present, there is no generally accepted theoretical framework in cognitive neuroscience for human affect and its regulation, neither is there a common understanding of their underlying neurobiological basis (Dalgleish, 2004; Lang & Davis, 2006; Phillips et al., 2003a). Subsequently, prominent experimental paradigms on affect (chapter 2.2.1.1) and its regulation (chapter 2.2.1.2) will be outlined. Of note, following Scherer (1984) and Gross (1998), affect in this thesis is the superordinate category for all valenced states including emotions and moods – emotions being more strongly object-related and temporarily restricted than moods.

2.2.1.1 Cognitive Neuroscience models on affect

The currently reigning experimental paradigm in cognitive neuroscience assumes that humans are endowed with a limited set of discrete, mutually independent emotions such as happiness, sadness, fear, each characterized by specific psychological, physiological and behavioral characteristics, and subserved by specific neural structures and pathways (Ekman, 1992, 1993; Panksepp, 1998a; Tomkins, 1962, 1963). However, attempts in localizing the neural substrates of specific emotions have rendered inconsistent results to date, with at times one and the same neural area being active in the processing of different emotions, and disparate basic emotions provoking similar physiological responses (for review see Dalgleish, 2004; Posner et al., 2005).

Alternatively, dimensional models of affect posit that emotions are presented in common neurophysiological systems. The circumplex model (Russell, 1980) as adapted by Posner (2005) for example proposes that emotions result from the cognitive appraisal of affective states, which arise from the linear combination of activity in two independent neurophysiological systems, one coding for valence and one for arousal (see Figure 2-8) (for a review on similar conceptualizations see Lang, 1995; Lang & Davis, 2006). Other such neurophysiologically-based dual-system models on affect break emotions down into approach and withdrawal components, behavioral activation or inhibition, appetitive versus aversive systems, or states elicited by the cognitive appraisal of two classes of reinforcing stimuli, rewards and punishments (e.g. Cloninger, 1987; Lang, Bradley, & Cuthbert, 1990; Ressler, 2004; Rolls, 2000) (see Figure 2-9). In all of these dimensional accounts, emotions are closely associated with the concept of rewards and punishments and the brain mechanisms supporting the behaviors associated with it - i.e. rewards being anything for which an individual will do work to obtain (i.e. approach), and a punishment anything for which it will do work to avoid or escape (i.e. withdraw) (Rolls, 2000).

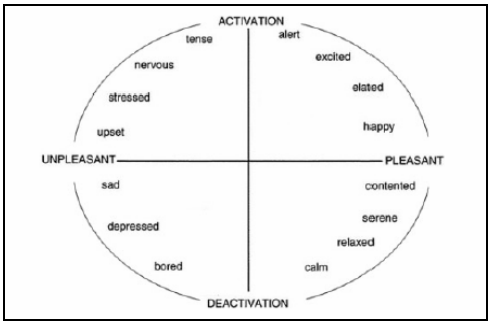

Figure 2-8: Graphical representation of the circumplex model of affect with the horizontal axis representing the valence dimension and the vertical axis representing the arousal dimension. From Posner et al. (2000).

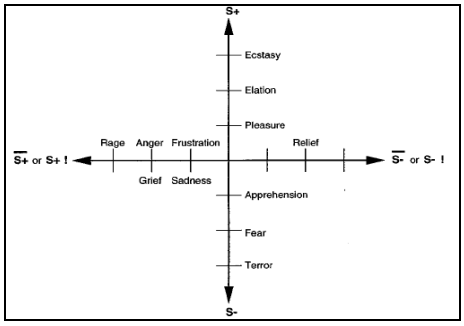

Figure 2-9: Emotions associated with different reinforcement contingencies. Intensity increases away from the centre of the diagram. S+/S- = presentation of a positive/negative reinforcer, $\overline{S+}/\overline{S-}$ = omission of a positive/negative reinforcer, S+!/S-! = termination of a positive/negative reinforcer. From Rolls (2000).

Human and translational animal research has consistently identified components of the mesocorticolimbic system in the identification and appraisal of the valence of a stimulus and the generation of an affective state and behavior in response to it. The mesocorticolimbic system encompasses a neural network consisting of dopaminergic neurons originating from the ventral tegmental area (VTA) of the midbrain, and their major projection sites in the limbic system (nucleus accumbens (NAcc), amygdala, hippocampus), and various regions within the prefrontal cortex (orbitofrontal cortex (OFC), medial PFC, Anterior Cingulate cortex (ACC)) (for review see Kelley & Berridge, 2002; Laviolette, 2007) (see Figure 2-10)

Midbrain dopaminergic neurons adjust dopamine release in response to anticipation or notification of emotionally salient events such as novel stimuli, natural (i.e. drugs, food or sex) as well as conditioned rewards, and aversive, punishing events (for review see Schultz, 2002). Dopamine release is initiated by glutamatergic inputs to the VTA from some of its major projection sites (i.e. NAcc, amygdala, PFC, and ACC). At the level of OFC, amygdala, and ACC dopamine may influence associative learning (i.e. associating two types of events) by imprinting stimulus-reward and response-reward associations (for review see Baxter & Murray, 2002; Holland & Gallagher, 2004; Laviolette, 2007; Rolls, 2004; Rushworth, Walton, Kennerley, & Bannerman, 2004). The OFC in addition has been implicated in coding for the hedonic value of a stimulus (Rolls, 2004), the ACC in error detection and conflict monitoring (for review see Bush, Luu, & Posner, 2000; Paus, 2001), and the amygdala in coding for the intensity/salience of sensory and social events and influencing arousal, presumably through its projections to brainstem nuclei, the hypothalamus, and/or the NAcc (for review see Anderson & Sobel, 2003; Dalgleish, 2004; Lang & Davis, 2006; Posner et al., 2005). At the level of the NAcc, dopamine may modulate inputs from other brain areas (e.g. the amygdala) and act as a “Go-Signal” for the initiation of motivated behavior such as appetitive, approach-related behavior or active avoidance behavior (for review see Panksepp, 1998b; Rolls, 2000). Motor output is influenced by GABAergic projections from the NAcc to downstream motor brain systems (i.e. thalamic nuclei, motor cortex).

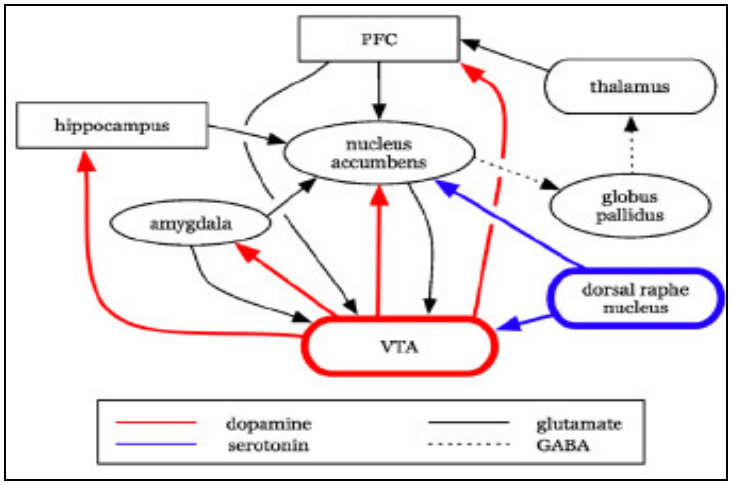

Figure 2-10: Schematic representation of the mesocorticolimbic system. Dopaminergic neurons from the ventral tegmental area (VTA) project to various subcortical regions (Nucleus Accumbens (NAcc), amygdala, hippocampus) and to the prefrontal cortex (PFC). The NAcc is a main component of this network, receiving reward-related information from the other regions to which the VTA projects. The VTa and NAcc in addition are influenced by 5-HT systems originating from the dorsal raphé nucleus in them midbrain. Serotonin from the dorsal rahpé nucleus acts to inhibit dopaminergically mediated effects. The major output pathway of the NAcc are GABAergic projections to the globus pallidus, influencing downstream motor regions and thus goal-related behavior. From Davey et al. (2008).

Several components of the mesocorticolimbic brain system undergo vast changes during adolescence (Chambers et al., 2003; Spear, 2000) (see also chapter 2.1.1). In addition, as illustrated in chapter 2.1.3, many contain steroid receptors and therefore likely are sensitive to the activating and/or organizational effects of hormones at puberty.

2.2.1.2 Cognitive Neuroscience models on affect regulation

A heuristic experimental paradigm in cognitive neuroscience that specifies the neural substrates underlying different steps of affect regulation based on a thorough review of the existing data has been proposed by Phillips, Drevets, Rauch, and Lane (2003a) (see Figure 2-11). According to this model, the *appraisal and identification* of the emotional significance (i.e. valence) of a stimulus, the *production of an affective state in response to it* - including autonomic, neuroendocrine, somatomotor (facial expression, tone, voice, verbalizations, or actions) responses and conscious emotional feeling - and the *automatic regulation* of these responses depend on a “ventral neural system”, consisting of several components of the mesocorticolimbic reward system. Further, the model proposes that *effortful emotion regulation* occurs by inhibiting or modifying activity in the ventral system by a “dorsal neural system” consisting of the hippocampus, dorsal regions of the ACC and PFC “so that the affective state and behavior produced are contextually appropriate” (Phillips et al., 2003a, pg. 504). According to Gross (1998) effortful emotion regulation may take place at all points of the emotion generative process, at the level of the stimulus (i.e. situation selection, modification), its cognitive appraisal (i.e. change of cognitions, deployment of attention), and emotion expression (i.e. modulation of responses).

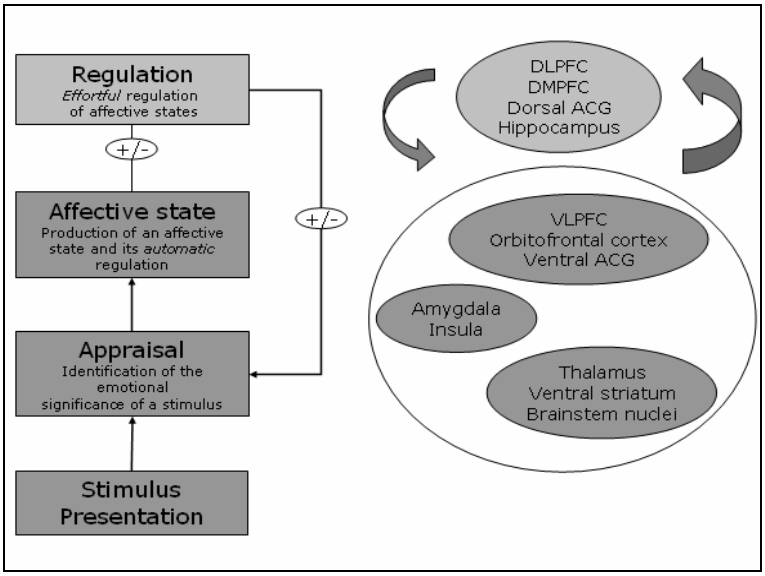

Figure 2-11: Left-hand side diagram: Relationships of the three stages of emotion processing. Right-hand side diagram: Neural structures implicated in emotion processing, and their putative functional relationships: A ventral system serves the identification of the emotional significance of a stimulus, the production of an affective state in response to it, and its automatic regulation (depicted in dark grey), whereas a predominantly dorsal system (depicted in pale grey) may regulate affective states and influence appraisals effortful. VLPFC, ventrolateral prefrontal cortex; DLPFC, dorsolateral prefrontal cortex; DMPFC, dorsomedial prefrontal cortex; ACG, anterior cingulated gyrus. From Phillips et al. (2003a).

The adaptive nature of emotion regulation is also accounted for in other neuroscientist's definitions. Dahl (2003, pg. 184) for example defines emotion regulation as "the subset of processes involved in the control of feelings – particularly the strategic control of feelings in the service of a goal or purpose … in adaptive ways. Typically, this modulation involves inhibition, delay, or altering emotional expression/behavior in ways that incorporate social rules, long-term goals, or avoiding future negative consequences." Thompson (1994, pg. 27-28) defines emotion regulation as consisting "of the extrinsic and intrinsic processes responsible for monitoring, evaluating, and modifying emotional reactions, especially their intensive and temporal features, to accomplish one's goals". For a more detailed review on emotion regulation, see Gross (1998).

2.2.2 Impulsivity and heightened-risk taking during adolescence

According to Moeller, Barratt, Dougherty, Schmitz, and Swann (2001, pg 1784), impulsivity may be defined as "a predisposition toward rapid, unplanned reactions to internal or external stimuli without regard to the negative consequences of these reactions to the impulsive individual or to others". Similarly, Chambers, Taylor et al. (2003, pg. 1042) conceptualize impulsivity as a "goal-directed behavior characterized by poor judgment in the attainment of rewards". Experimental paradigms examining impulsivity operationalize it either as the perseverance of a response that is unrewarded or punished, suboptimal decision-making characterized by the preference of a small immediate reward over a greater delayed reward, making premature responses, or inability to withheld responses (for review see Moeller et al., 2001). Thus, following these definitions and operationalizations, impulsive

behavior may be viewed as one behavioral expression of insufficient affect regulation – the strategic control of feelings and impulses in service of long-term adaptive goals (see chapter above).

In terms of the neural mechanisms underlying impulsivity during adolescence, most developmental cognitive neuroscientists concur with the notion that maturational transitions in the brain affecting cognitive-regulatory and/or affective neural systems may predispose adolescents to impulsive behavior; however, there is less agreement on which specific neural substrates and mechanisms are in fact at work, giving rise to different theoretical conceptualizations. While some neuroscientists focus on "top-down" control of behavior, for example suggesting that the late maturation and functional integration of parts of the PFC lead to impaired inhibitory capacity or disregard of long-term consequences of an action (chapter 2.2.2.1), others emphasize more strongly "bottom-up" influences on behavioral output, suggesting that enhanced (chapter 2.2.2.2) or reduced activity at the level of the NAcc (chapter 2.2.2.3), and/or reduced activity of the amygdala (chapter 2.2.2.4) may lead to increased impulsivity during adolescence.

2.2.2.1 Maturing prefrontal cognitive control

Adolescence is characterized by a steady improvement in several cognitive abilities such as working memory, strategic planning or inhibitory control that depend on integrative function of the PFC with other task-specific cortical and subcortical brain regions (see chapter 2.1.2). Two such steadily improving cognitive functions and their underlying neural substrates have been proposed by developmental neuroscientists to be of particular relevance for impulsive behavior during adolescence, namely inhibitory control (i.e. the ability to inhibit context inappropriate but prepotent response tendencies), and the ability to link behaviors with their outcomes and consequences (i.e. one form of associative learning). Luna and Sweeney (2004, pg. 306) for example have suggested, that "the lack of efficient brain integration may account for some behavioral characteristics of adolescence, such as being driven by external stimuli that overcome the still unstable systems for the voluntary control of behavior (impulsivity)." Yurgelun-Todd (2007, pg. 255) states that "the maturation of prefrontal networks plays a critical role in the cognitive and emotional behaviors displayed by adolescents." Crone, Bunge, Latenstein, and van der Molen (2005) finally propose that adolescents engage in risky behaviors because the late development of the PFC, in particular its ventral and medial parts, would prevent them from anticipating the long-term outcomes of their actions, resulting in a "myopia for the future" (Crone et al., 2005, pg. 261) and thus leading to a natural tendency to base decisions on short-term outcomes. As reviewed below, the few fMRI studies investigating differences between adolescents and adults during processing of emotionally evocative information indeed document developmental differences in PFC activation, with adolescents showing more diffuse activation patterns than adults (e.g. Galvan et al., 2006; Levesque et al., 2004; Monk, Grillon et al., 2003).

2.2.2.2 Enhanced activity at the level of the NAcc

Chambers and colleagues (Chambers & Potenza, 2003; Chambers et al., 2003) take a more bottom-up focus on adolescent impulsivity by proposing that during adolescence, robust dopaminergic activity at the level of the NAcc combined with insufficient inhibitory control from the PFC and 5-HT (serotonin) system results in a pro-motional motivated state that may facilitate approach behavior (see Figure 2-12).

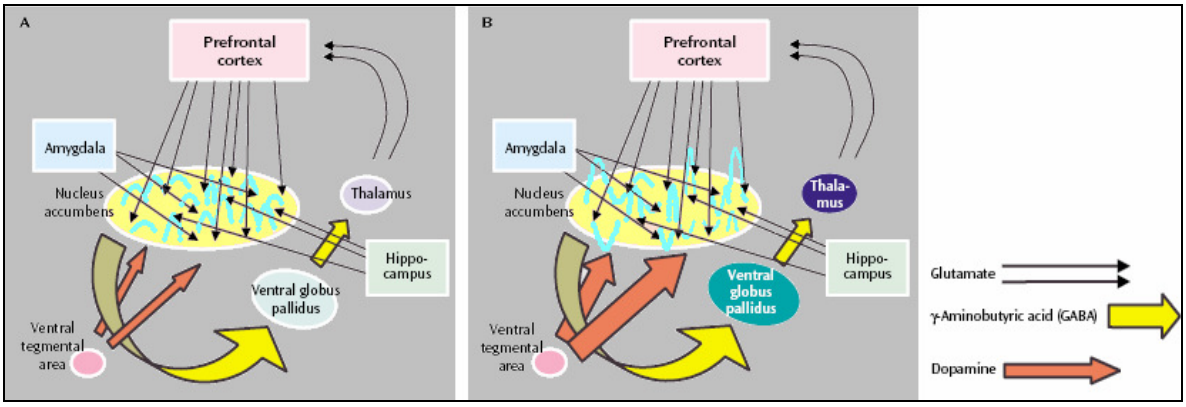

Figure 2-12: Neural model of adolescent behavioral propensities. From Chambers et al. (2003).
Part A: Motivated behavior is subserved by a neural circuit composed of cortico-striatal-thalamo-cortical loops that can be influenced at the level of the NAcc by affective, sensory or contextual memory information from surrounding brain areas such as the hippocampus and the amygdala.
Part B: During adolescence, increased dopamine input into the NAcc (thickened red arrows) in conjunction with ongoing PFC maturation may increase firing patterns of NAcc neurons in response to cortical and limbic glutamatergic input - depicted as increases in local peak amplitudes – facilitating behavioral responses in downstream motor systems (ventral globus pallidus, thalamus and (sub)cortical centers of motor output) to novel or rewarding stimuli such as drugs, sex, food.

This view of enhanced activity at the level of the NAcc during adolescence as compared to other age groups is supported by several fMRI studies investigating the neural substrates of reward processing in different age groups. Galvan et al. (2006) for example investigated brain activation in 16 children (mean age 9.8 years), 13 adolescents (mean age 16 years), and 12 adults (mean age 25 years) on a reward task. Subjects had to indicate the side of the screen on which one of three cues, each associated with a different amount of coins, was presented. Results showed that all subjects activated the orbitofrontal cortex (OFC) and NAcc during execution of correct trials to the highest rewards, however OFC activation was more diffuse in adolescents and children as compared to adults, and NAcc activation was significantly stronger in adolescents as compared to children or adults (see Figure 2-13). The authors interpreted these findings as that “NAcc development may precede that of OFC during adolescence” (Galvan et al., 2006, pg. 6889). Of note, not only neural activity, also reaction time was modulated by reward, i.e. adults and, albeit to a smaller degree, adolescents, but not children, showed a modulation of reaction time depending on reward magnitude, with faster reaction time for higher rewards. Finally, NAcc activity was positively correlated with the likelihood of engaging in risky behavior as indexed by self-ratings in all age groups (Galvan, Hare, Voss, Glover, & Casey, 2007).

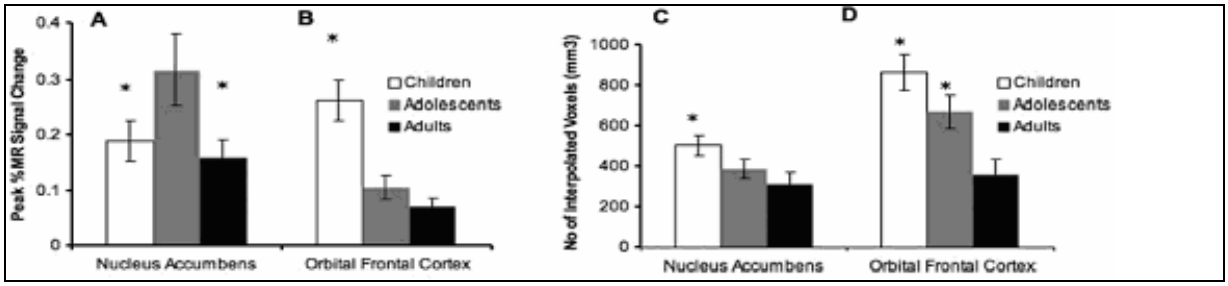

Figure 2-13: Panels A and B: Magnitude of NAcc and OFC activity differs between age groups. A: In NAcc, adolescents showed significantly greater percent change in MR signal from baseline to the large reward condition than children and adults. B: In OFC, children had the greatest percent change in MR signal relative to adolescents and adults.
Panels C and D: Extent of activity becomes more focal with age in both, NAcc and OFC. C: Children showed significantly larger volume of activity in the NAcc relative to adolescents and adults. D: Children showed significantly greater volume of activity in the OFC than adolescents who showed significantly greater volume of activity than adults. Error bars indicate SEM. * denote significant activation differences. From Galvan et al. (2006).

Similar results have also been reported by Ernst, Nelson, Jazbec et al. (2005) and May et al. (2004). Ernst et al. (2005) investigated brain activation in 16 adolescents (mean age 13.3) and 14 adults (mean age 26.7) after notification of winning or not winning a monetary reward. Results indicated greater increase of activity in the left NAcc of adolescents as compared to adults when winning $4 and stronger reduction of activity when not winning $4. Moreover, adolescents reported greater intensity of positive feelings when winning than adults and these reports covaried significantly with reward-related activation in the right NAcc. In contrast, adults showed greater MRI signal intensity changes than adolescents when winning and not winning $4 in the left amygdala (see Figure 2-14).

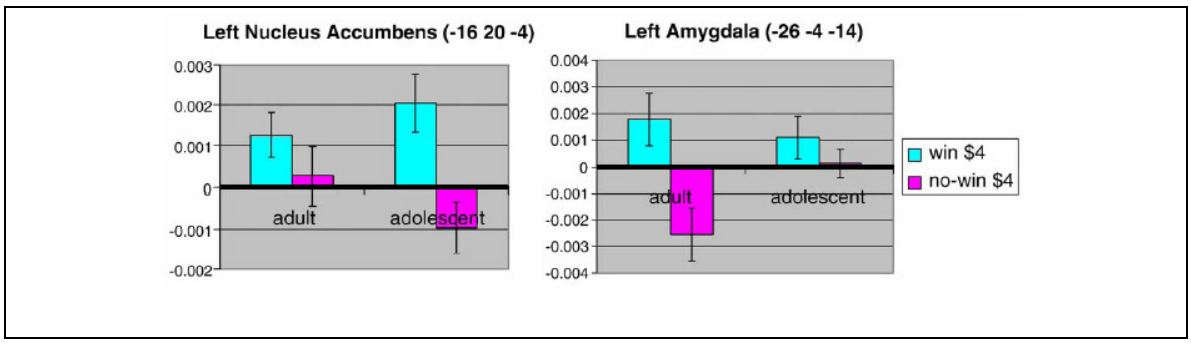

Figure 2-14: Mean (+SE) BOLD signal intensity changes between notification of winning respectively not winning 4$ relative to baseline for the left NAcc and for the left amygdala respectively. Each condition ([win $4 vs. fixation] in blue and [no win 4$ vs. fixation] in magenta) is represented separately for adults and adolescents. Adapted from Ernst et al. (2005).

May et al. (2004) investigated neural responses to positive, negative or no monetary outcomes (winning 1$, losing 0.5$, or no money) in a simple guessing task in 12 healthy adolescents (mean age 13.25). Subjects had to guess if a question mark ("?") would turn into a number greater or smaller than 5. Results revealed activation of the ventral striatum (including NAcc) and OFC during processing of reward-related information in adolescents, with larger responses to positive (winning money) than negative feedback (losing money). However, this study did not include other age groups, which precludes statements about developmental differences in reward processing.

2.2.2.3 Decreased activity at the level of the NAcc

In contrast to the research groups around Chambers (Chambers & Potenza, 2003; Chambers et al., 2003) and Ernst (Ernst et al., 2005; Ernst et al., 2006), both of which endorse enhanced activity of the NAcc during adolescence, other authors such as Spear (2000) and Bjork et al. (2004) propose that NAcc activity is *diminished* during adolescence, based on rodent data indicating decreased dopamine transmission in the NAcc during adolescence. This may lead to a temporary "reward-deficiency syndrome" (Spear, 2000, pg. 446), forcing adolescents to approach more robust incentives (such as risk taking or drug experimentation) to recruit this circuitry and thus attain positive arousal (Bjork et al., 2004; Spear, 2000). There is one fMRI study conducted by Bjork et al. (2004) supporting this notion. Specifically, the authors examined brain activation during anticipation and outcome notification in a delayed response task in 12 adolescents (mean age 14.75 years) and 12 adults (mean age 23.8 years). Subjects had to react to the appearance of a target cue within a specified time window in order to win or to avoid losing money (see Figure 2-15). Results indicated no difference in hit rate or reaction time between different monetary conditions or groups. Anticipation of responding for gain (all amounts collapsed) as compared to the non-incentive condition activated in both age groups the NAcc, albeit and in contrast to results obtained by Ernst et al. (2005) and Galvan et al. (2006) less so in adolescents than adults. Anticipation of responding to avoid loss as compared to the non-incentive condition did also activate the NAcc in both groups, especially in trials with high monetary stake such as avoiding losing $5, but overall activation was smaller than during anticipation of responding for potential gain. Notification of outcome activated the medial prefrontal cortex for gain and deactivated it for losses at similar levels in adults and adolescents.

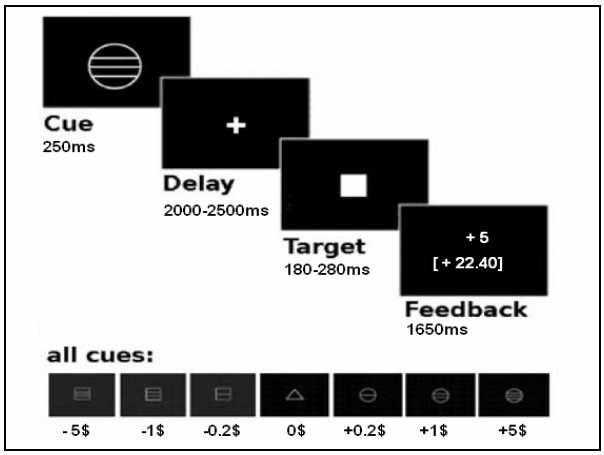

Figure 2-15: Schematic diagram of the Monetary Incentive Delay (MID) task adapted from Juckel et al. (2006).
1) One of 7 cues presented for 250ms indicates the stake of the trial: Three reward cues (circles with either one, two or three lines) signal potential monetary reward (0.2$, 1$ or 5$); three punishment cues (squares with either one, two or three lines) signal potential monetary loss (0.2$, 1$ or 5$); and one control cue (triangle) signals a non-incentive trial.
2) After a random time interval of 2000-2500ms,
3) the target appears, a white small square prompting subjects to press as fast as possible a button in order to obtain reward resp. avoid loss.
4) Finally, feedback is provided indicating trial outcome and cumulative earnings.

2.2.2.4 Decreased activity of harm avoidant brain systems

Ernst, Pine, and Hardin (2006) draw attention to the fact that risk-taking may not only result from enhanced responsiveness to rewarding or novel stimuli, but also of decreased aversiveness to potentially negative or punishing stimuli. In their "triadic model of the neurobiology of motivated behavior" they propose that motivated behavior results from the balanced engagement of three behavioral/neural systems: 1) A reward-seeking approach system, supported by a neural network encompassing the dorsolateral part of the prefrontal cortex, the ventral striatum including the NAcc and dopamine; 2) a harm avoidant system, supported by a neural network encompassing the amygdala, the temporal pole, and serotonin, and 3) a regulatory system, supported by the ventral/medial part of the prefrontal cortex, that balances the action of the approach-driven and harm-avoidant systems. During adolescence, Ernst et al. (2006) propose that the activity of the reward system prevails over that of the avoidant system while the still immature regulatory systems fails to adaptively balance these two behavioral controllers (see Figure 2-16). However, the model does not specify if the loci of maturational lag lay within these circuits, in their functional connectivity, or in both. In support of the triadic model, Ernst et al. (2005) found in their fMRI study (see chapter 2.2.2.2 above), less impact of negative outcomes (not winning money) on amygdala activation in adolescents as compared to adults.

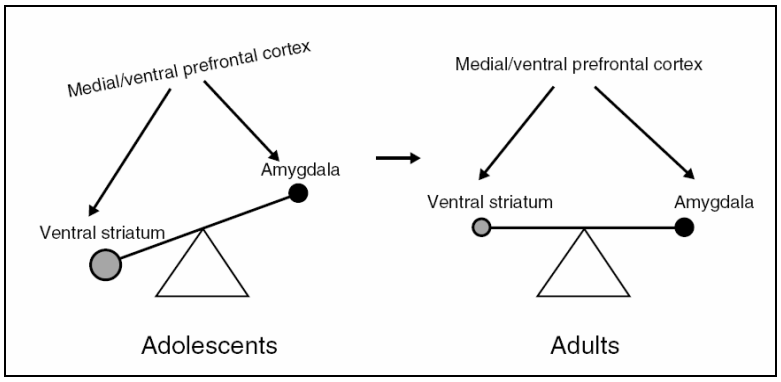

Figure 2-16: Triadic model of adolescent behavioral propensities. The model proposes that the balance between reward-driven and harm-avoidant behavior is tilted toward reward-driven in adolescents as compared to adults. This pattern may result from a stronger reward-related system, weaker harm-avoidant system, and/or poor regulatory control. From Ernst et al. (2006).

2.2.3 Emotional distress and affective disorders during adolescence

Analog to impulsivity, developmental neuroscientists explain negative affective states during adolescence as resulting from maturational changes in the adolescent brain affecting cognitive-regulatory, and/or affective-arousal systems, and/or their integration. In Table 2-1 some affective adjustment problems are summarized that may arise during adolescence due to specific maturational transitions in the brain. Since this thesis is thematically based on the functional relationship of regulatory and affective brain systems during adolescence, models specifically involving affect will be outlined in more detail (see chapter 2.2.3.1.1), followed by a section addressing the factors that may render an individual vulnerable to the development of mood and anxiety disorders (see chapter 2.2.3.2).

Table 2-1: Selected areas in which adjustment problems may arise during adolescence leading to negative mood states such as anhedonia, anxiety, dysphoria, embarrassment, and their hypothesized neural underpinnings, with respective references.

Developmental area		Possible maladjustment	Possible neural correlates	Selected References
Cognitive development	Increasing capacity for abstract thinking Development of social cognition and mentalizing abilities	Adolescents may envision more future threats Increased capacity for rumination Increasing ability to envision other people's mental states may lead to heightened self-awareness and embarrassment	Maturation of the "social brain" in particular the medial PFC and superior temporal sulcus	Larson and Ham (1993); Larson and Richards (1994); Rosso, Young, Femia, and Yurgelun-Todd (2004); Moriguchi, Ohnishi, Mori, Matsuda, and Komaki (2007); Nolen-Hoeksema, Stice, Wade, and Bohon (2007); Blakemore (2008a; 2008b)
	Pursuit of more abstract, long-term goals and rewards	Abstract rewards are more tenuous and easily frustrated	Integration of PFC with the dopaminergic reward system	Davey, Yucel, and Allen (2008)
Affect regulation	Affective systems dominate emotional state/ behavioral output Affect regulation skills increase slowly with age and experience	Reduced positive affect may lead to anhedonia, and depression	"Reward-deficiency syndrome"	Spear (2000)
			Maturation of mesocorticolimbic brain system	Forbes and Dahl (2005); Forbes, et al. (2006)
		Increased negative affect Attentional bias for negative and threatening information	Functional developmental changes in PFC-amygdala circuitry	Monk et al. (2003); Skuse, Morris, and Lawrence, (2003); Lonigan, Vasey, Phillips, and Hazen (2004); Pine, (2007)
		Heightened sensitivity to social stimuli	"Affective neural node" matures before "regulatory neural node"	Nelson, Leibenluft, McClure, and Pine (2005)
		Risk-Taking, Risk-Avoidance	Regulatory system may not balance influence of appetitive and harm avoidant neural systems	Ernst, Pine, and Hardin (2006)
Puberty	Enhanced stress sensitivity	Negative life events may have more impact, overwhelm the adolescent	HPA-hyperactivity at puberty onset, and its influence on affective neural systems	Cameron (2004); Walker, Sabuwalla, and Huot (2004); Young and Altemus (2004); Romeo and McEwen (2006)

2.2.3.1 Dysregulation of affective states during adolescence

In developmental psychology and psychopathology attempts have become popular which explain the increased negative mood reported by adolescents as compared to adults and children (see chapter 1) as an expression of insufficient and/or derailed affect regulation (Forbes & Dahl, 2005). This approach is supported by behavioral data indicating less use of affect regulation strategies in adolescents as compared to adults (Folkman et al., 1987; Gross et al., 1997) and an interrelation between emotional and behavioral problems during adolescence, and affect intensity and/or regulation (e.g. Graber & Brooks-Gunn, 1995; Larson, Raffaelli, Richards, Ham, & Jewell, 1990; Sheeber, Allen, Davis, & Sorensen, 2000; Silk, Steinberg, & Morris, 2003). Yet, many of these models lack specificity in terms of which aspects of affect may be dysregulated in what way (Forbes & Dahl, 2005; Pollak, 2005) (for different aspects of affect that may be dysregulated, see Figure 2-17). Similarly, developmental neuroscientists globally apply the framework of a maturational dysbalance between regulatory and affective neural systems to externalizing (i.e. impulsive, hyperactive, and aggressive behaviors, see chapter 2.2.2) and internalizing (i.e. withdrawn, anxious, and depressed, social withdrawal) problems during adolescence, often without specifying the particular aspects of affect that are being deregulated, their precise neural underpinnings, and often without distinguishing between transient adjustment problems and the expression of clinical disorders such as depression and anxiety disorders (e.g. Dahl, 2003, 2004a; Kelley, Schochet, & Landry, 2004; Steinberg, 2004, 2005).

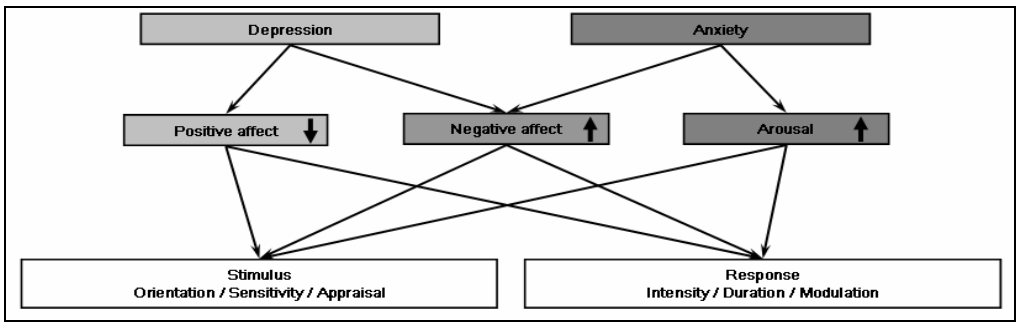

Figure 2-17: Different aspects of affect dysregulation that may be involved in adolescent depression and anxiety. In depression, positive affective states may be decreased, and/or negative affective states such as sadness or irritability may be enhanced. In anxiety, negative affective states such as anxiety and fear may be increased, possibly leading to hyperarousal. For all affective states, the dysregulation may take place at the stimulus perception and/or response level. For example, there may be an elevated threshold to activate positive affect and/or a less intense or volatile response once positive affect is activated. In addition, or alternatively, there may be a lower threshold to activate negative affect, or a longer or more intense response once negative affect is activated. In anxiety, there may be a lower threshold to activate fear and/or a more intense or sustained response once fear is activated.

In this chapter, first two integrative developmental neuroscience models on affect dysregulation as a platform on which adolescent emotional turmoil may develop are outlined (see chapter 2.2.3.1.1). Subsequently, two specific components of affect that may be dysregulated in adolescent mood and anxiety disorders that have recently drawn attention in cognitive developmental neuroscience research will be presented, namely reduced positive affect, and increased attention allocation towards threatening or negative information (see chapters 2.2.3.1.2 and 2.2.3.1.3).

2.2.3.1.1 Integrative accounts

Two integrative neuroscience-based models on affect regulation in adolescent negative mood have been proposed by Ernst et al. (2005) and Nelson et al. (2005).

Nelson et al. (2005) propose that during adolescence, disjunction in the maturation of two nodes of a larger neural network involved in the processing of social information, namely a puberty-sensitive "*affective node*" based on limbic brain structures and a late maturing "*cognitive-regulatory node*" based on the PFC, lead to a transition phase in which affective responses to individually-relevant social events are enhanced, yet not tempered by regulatory mechanisms. This maturational mismatch is said to explain heightened emotional lability and reactivity during adolescence, with the quality of the social event determining the direction of the mood swing, i.e. pleasant social events will lead to strong positive, and negative events to strong negative feelings. Extreme activity within the affective node, for example brought about by distressing interpersonal experiences, may according to the model be particularly relevant for the development of maladjustment. Indeed, negative social events play a major role in the development of emotional difficulties during adolescence. For example, rejection by romantic partners and peers is one of the strongest predictors for the emergence of an initial depressive episode and suicide attempts (Hecht, Inderbitzen, & Bukowski, 1998; Monroe, Rohde, Seeley, & Lewinsohn, 1999; Prinstein & La Greca, 2004; e.g. Vernberg, 1990).

Ernst et al. (2005) apply their "triadic model" (see chapter 2.2.2.4) also to adolescent negative mood states. Specifically, the authors propose that in adolescent depressed or anxious mood, *activity of the approach system based on the NAcc may be reduced* and/or *activity within the harm avoidant system based on the amygdala increased*, which may, given *reduced modulatory control by the maturing PFC*, result in anhedonia, loss of energy, amotivation, and/or risk avoidance. In less severe conditions, the authors suggest that the approach system may also become overactive, as an expression of hyperarousal (in anxiety) or in an attempt of short-term affect regulation. This notion is supported by research indicating that adolescents with emotional distress show a higher rate of short-term rewarding impulsive behaviors such as eating fatty foods or drug abuse than controls (for review see Pechmann et al., 2005; Tice, Bratslavsky, & Baumeister, 2001) (see also chapter 1.2.4).

Only few fMRI studies examined brain activation in adolescents while regulating *distressing* emotions. However, these studies do support the notion of reduced PFC regulatory control over (overactive) neural systems involved in mediating affective states. Monk et al. (2003) for example showed that adolescents exhibit greater activity than adults in the amygdala, OFC, and ACC when viewing fear evoking faces. When asked to switch attention between an emotional property ("How afraid does it make you feel?") and a non-emotional property of the face ("how wide is the nose?"), only adults, but not adolescents were able to selectively engage and disengage the OFC. The authors suggest that these results indicate greater bottom-up influence on information processing in adolescents as compared to adults. In a study by Lévesque et al. (Levesque et al., 2003; Levesque et al., 2004), voluntary suppression of sadness activated more prefrontal cortical areas in girls (mean age 9.9 years) than women, according to the authors reflecting immaturity of the prefronto-limbic connections in childhood.

2.2.3.1.2 Decreased positive affect

In contrast to Ernst et al. (2005) and Nelson et al. (2005), Forbes and Dahl (Forbes et al., 2006; 2005; Forbes, Shaw, & Dahl, 2007) take a more specific approach by focusing on one aspect of affect that a) may be dysregulated in adolescent mood and anxiety disorders and b) can be mapped onto a specific neural substrate. Specifically, they suggest that depressive states during adolescence reflect a reduction in positive affect. Adhering to the cognitive neuroscience perspective on affect and its regulation (see chapter 2.2.1), positive affect in this concept is a construct related to reward-processing, encompassing subjective affective experiences (enjoyment of rewards), affective behaviors (work to obtain anticipated rewards), and accompanying physiological responses.

The notion of reduced positive affect in depression is not a new one. For example, several affective models on adult depression propose that depressed individuals experience diminished positive affect ("tripartite modely" by Clark & Watson, 1991), less positive social reinforcement (Lewinsohn, Hoberman, Teri, & Hautzinger, 1985), and exhibit reduced appetitive activity (Depue & Collins, 1999; Depue & Iacono, 1989; e.g. Fowles, 1988). Indeed, several symptoms considered typical for depression can be conceptualized within a low positive affect framework: While anhedonia signifies the reduced capacity to experience enjoyment, other symptoms such as social withdrawal, loss of libido, loss of appetite, and/or general fatigue may reflect diminished motivation to pursue natural or conditioned rewards (Forbes & Dahl, 2005).

Empirically, diminished positive affect is documented in *self-reports* of depressed adults (e.g. Watson, Clark, & Carey, 1988; Watson et al., 1995) and adolescents (Chorpita, 2002; Forbes, Williamson, Ryan, & Dahl, 2004; e.g. Joiner, Catanzaro, & Laurent, 1996; Joiner & Lonigan, 2000). Behaviorally, there is evidence for *reduced physiologic responses to rewarding stimuli* (Rottenberg, Kasch, Gross, & Gotlib, 2002; Sloan, Bradley, Dimoulas, & Lang, 2002; Sloan, Strauss, Quirk, & Sajatovic, 1997; Sloan, Strauss, & Wisner, 2001), and *failure to exhibit a response bias for monetary rewards* in adults with depression or low mood scores (Henriques & Davidson, 2000; Henriques, Glowacki, & Davidson, 1994; Hughes, Pleasants, & Pickens, 1985; Pizzagalli, Iosifescu, Hallett, Ratner, & Fava, 2008; Pizzagalli, Jahn, & O'Shea, 2005). In depressed and anxious youth, to my knowledge, prior to the data presented in this thesis (Jazbec, McClure, Hardin, Pine, & Ernst, 2005), no study explicitly investigated reward-related behavior. However, one study showed that selective attention of healthy, but not of depressed or anxious adolescents is disrupted by positive stimuli, which according to the authors suggests “that a common underlying feature of pediatric affective disorders such as anxiety and depression may be alterations associated with processing positive emotional information” (Ladouceur et al., 2005, pg. 174). A recently published study (Forbes et al., 2007) investigated reward-related decision-making in 221 11-year old-boys, 25 of whom had a depressive disorder and 38 an anxiety disorder. Results indicated that the depressed but not the anxious boys showed peculiarities in reward-processing; specifically they failed to choose options with high probability of yielding a high magnitude reward. Moreover, this lack of responding for gains predicted diagnosis of depressive symptoms, and depressive disorders with and without comorbid anxiety disorders one year

later. The authors interpreted the findings as either indicating diminished motivation to obtain future reward in the depressed boys, or as poor flexibility in shifting behavior when contingencies change, since choosing the low gain option was advantageous on trials with a low probability of winning (Forbes et al., 2007).

In terms of the neural substrates underlying reduced positive affect in adolescent depression, Forbes and Dahl (2005) suggest dysfunction in the brain's mesocorticolimbic reward system (for review on the mesocorticolimbic system see chapter 2.2.1.1), such as decreased levels of activation in reward-related brain regions during anticipation or after receipt of reward, lack of differentiation between large and small rewards, and/or impairments in dopamine function (for similar hypotheses on adolescent anhedonia, see Ernst et al., 2006; Spear, 2000). fMRI studies offer support for this notion. Forbes et al. (2006) for example investigated neural activity during a reward-related decision-making task in depressed adolescents, many with comorbid anxiety disorders, adolescents with an anxiety disorder, and controls. In comparison with controls, depressed adolescents exhibited diminished activity in the ACC, ventral OFC, and striatum (bilateral caudate nucleus) and increased activity in the dorsal OFC during anticipation for responding for reward. Interestingly, also the anxious adolescents showed dysfunction in reward-related brain regions, with more variable, but also more extreme responses than depressed adolescents. This finding is corroborated by a recent study by Guyer et al. (2006), reporting greater striatal activation to incentives in behaviorally inhibited adolescents than in non-inhibited adolescents. Of note, behavioral inhibition has been considered an important temperamental risk-marker for the development of affective disorders (Pine, 2007) (see chapter 1.3.5).

2.2.3.1.3 Increased negative affect: Attentional bias for threatening or negative information

One prominent affective model on adult mood and anxiety disorders is the tripartite model by Clark and Watson (1991) which proposes that depression is characterized by a decrease in positive affect, anxiety by physiological hyperarousal, and both depression and anxiety by an increase in negative affect which represents the displeasurable engagement with the environment and a sense of high subjective stress. The research group around Lonigan has adopted the notion of low positive and high negative affect in youth and propose that high levels of negative affect in conjunction with low levels of executive control represents a major risk factor for the development of an anxiety or depressive disorder, depression additionally being associated with low positive affect (for review see Lonigan et al., 2004). Thus, a child with high negative affect but high executive control will have a smaller probability to develop an internalizing disorder than a child with high negative affect and low executive control. In addition, the authors propose that this combination of high negative affect and low executive control is reflected in an attentional bias for threatening or negative stimuli.

Indeed, there is a vast body of literature documenting cognitive biases in adult and adolescent patients with depression and anxiety. Specifically, while patients with anxiety have been shown to exhibit heightened acquisition and/or diminished extinction of learned fear, attention allocation towards

threats (and away from threats as their intensity increases), and interpretation of emotionally ambiguous stimuli as threatening (for review see Bishop, 2007; Mogg & Bradley, 1998; Pine, 2007), patients with depression have been reported to show a cognitive bias in encoding respectively recalling of negative events, but not an attentional bias (Caseras, Garner, Bradley, & Mogg, 2007; e.g. MacLeod, Mathews, & Tata, 1986; Siegle, Granholm, Ingram, & Matt, 2001; Silk et al., 2007).

Two interconnected components of the mesocorticolimbic brain system have consistently been implicated in processing of threats or negative information; the amygdala and the PFC, in particular the ventrolateral PFC. The current view is that the amygdala is critical for recruiting and coordinating cortical arousal and attention allocation to stimuli which are considered as important for the organism's survival, while the PFC has been implicated in the regulation of such responses (Dalgleish, 2004; for review see Phillips et al., 2003a). In anxious and depressed individuals, evidence suggests disruption in the function of both, amygdala and PFC, with *amygdaloid hyper-responsivity* and *deficient recruitment of prefrontal regulatory mechanisms* during threat-related or negative information processing (for review in adults see Bishop, 2007; R. J. Davidson, Pizzagalli, Nitschke, & Putnam, 2002; for review in youth see Pine, 2007). Supporting the hypothesis of Lonigan et al. (2004) of an interaction between executive control and negative affect, there seems to be a functional relationship between these two brain areas, with higher prefrontal recruitment, for example due to performance of a cognitively demanding task, leading to decreased feelings of anxiety and distress and decreased subcortical activation (McClure et al., 2007; Monk et al., 2008; Monk, McClure et al., 2003). Disruption of the amygdale-prefrontal circuitry has also been put forward to explain the above mentioned typical cognitive biases observed in anxious and depressed individuals.

2.2.3.2 Transient versus permanent maladjustment

For most adolescents, affect regulation difficulties diminish with age, and the majority of young adults show significant improvements in behavioral control, positive affect, and self-confidence (B. W. Roberts, Caspi, & Moffitt, 2001). For some adolescents however, adjustment problems escalate to the level of depression or clinical anxiety, with their high continuity into adulthood and impairment in psychosocial functioning (see chapters 1.2.4, 1.3.4). Several neurally mediated factors seem relevant in conferring risk of developing an affective disorder in adolescence: *Genetic predisposition*, activated by pubertal hormones or other maturational brain processes (for review see Walker et al., 2004), enhanced *impact of environmental stressors on neural circuits undergoing maturational reorganization* (for review see Luna & Sweeney, 2004; Pechmann et al., 2005), and/or *timing of puberty-onset in relation to hormone-independent brain maturation* (for review see Dahl, 2004a; Sisk & Foster, 2004).

2.3 Synopsis chapter 2

Over the past decade, application of magnetic resonance imaging techniques has enabled neuroscientists to examine adolescent structural and functional brain maturation. Evidence indicates profound re-organization of brain systems involved in the regulatory control of cognitive functions, affective states and behaviors, which in some brain regions such as the prefrontal cortex continues well into adulthood. On the other hand, puberty-onset at the beginning of adolescence leads to a surge of hormones that is swamping the adolescent brain, affecting brain systems mediating sexual reproduction and the behavioral, motivational and social skills required for it.

Cognitive developmental neuroscientists have employed these maturational changes of the adolescent brain to explain adolescent behavioral propensities. Although differing in details and specific brain regions at focus, most integrative cognitive developmental neuroscience models propose that the mismatch in maturation of regulatory and affective brain systems during adolescence leads to a period of natural affect dysregulation, in which strong impulses and affects are not yet tempered by cognitive control skills. Thus, according to this view, adolescent impulsivity may reflect the inability to use long-term adaptive goals to guide momentary affective needs and behaviors, while emotional turmoil may reflect the inability to use cognitive regulatory skills such as attention allocation or cognitive restructuring to readjust and balance emotional states. In addition, in conjunction with genetic predispositions and/or stressful life events, this period of heightened experience-dependant plasticity of regulatory-affective brain regions may result in permanent alterations in neural structure that predispose an individual for recurrent affect regulation impairments later in life. Form this background, the investigation of functional and structural brain maturation during adolescence may provide important insights in the development of affective disorders and possibly offer an informative basis for the development of earlier and more focused intervention strategies.

Yet, despite the advances in developmental cognitive neuroscience, the specific neural mechanisms underlying adjustment problems in adolescence, and their transition into manifest mood and anxiety disorders are still unclear, to date allowing only global statements on affect dysregulation. To further advance the field, more focused research, parsing complex psychological constructs into investigational components that can be mapped onto neural circuits, are of importance. One such promising approach is the study of reward-related information processing, since 1) the processing of rewards is crucially intertwined with the concept of affect in cognitive neuroscience, such that rewards lead to positive affect and approach behavior (as characteristic for impulsivity), and punishments or threats to negative affect and/or avoidance behavior (as characteristic for anxiety and depression), 2) the neural substrates underlying reward-processing are well understood, 3) these neural substrates are among those that undergo vast maturational changes during adolescence, and 4) healthy adolescents as well as those with mood and anxiety disorders show peculiarities in reward-processing and brain activation during reward-processing, suggestive of increased or decreased reward sensitivity, and/or increased or decreased punishment sensitivity in healthy adolescents, respectively adolescents with mood and anxiety disorders.

In addition, besides specifying more precise behavioral components for further investigation, other neuroscience-based methods besides fMRI should complement the emerging picture on adolescent functional brain maturation. Although use of fMRI has advanced the field of developmental cognitive neuroscience in the past decade immensely by providing data on brain regions activated during information processing in pediatric populations (for review on the use of fMRI in pediatric populations, see for example M. C. Davidson, Thomas, & Casey, 2003; Gaillard, Grandin, & Xu, 2001), it has a slow response time in the range of seconds. Events occurring in the range of tens or hundreds of milliseconds can not be precisely mapped onto neural substrates by means of this technique. In the next chapter, the investigation of saccadic eye movements as a quantitative measure of the temporal characteristics of information processing as a complementing investigational means to fMRI will be introduced.

3. Saccadic eye movements as a research tool

Saccades are rapid (up to 600° visual angle per second), brief (around 20 to 30ms duration), accurate eye movements that direct the fovea – the part of the eye with best visual acuity- to capture points of interest in the environment (Leigh & Kennard, 2004; Ramat, Leigh, Zee, & Optican, 2007). Unrestrained, saccadic eye movements have been used in cognitive neuroscience as an index of overt attention allocation (Fischer, Biscaldi et al., 1997; Gottlieb, 2007). In addition, saccadic eye movements have been integrated in different task paradigms probing specific cognitive functions such as spatial working memory or executive cognitive control, for example by asking subjects to look at (different) remembered location(s) or to inhibit a gaze towards a novel, but task-irrelevant event (see Figure 3-1) (for review see Broerse et al., 2001).

Depending on their application, saccadic eye movements recruit a more or less extensive neural network consisting of cortical and subcortical areas. The neural underpinnings of the specific temporal and spatial characteristics of different saccade types (e.g. voluntary, involuntary) have increasingly been delineated in the last 30 years using multiple techniques from the single neuron level in non-human primates to functional imaging and lesion studies in humans, allowing cognitive neuroscientists to map saccade performance parameters to the function of specific neural correlates. In this chapter, the use of saccadic eye movements as a research tool for investigating the cognitive control of behavior (chapter 3.1) in development (chapter 3.3), in affective disorders (chapter 3.4) and in conjunction with reward-related information processing (chapter 3.5) will be addressed in more detail, as well as its underlying neural circuit (chapter 3.2).

3.1 The antisaccade task paradigm

In the antisaccade (AS) task paradigm, subjects are asked to perform eye movements towards the mirror location of a peripherally presented target relative to a central fixation point, referred to as antisaccades (see Figure 3-1, panel B). The AS task has been introduced by Hallett in 1978 in order to investigate the extent in which eye movements can be influenced voluntarily. In the 1980's the AS task has increasingly been employed as a means to examine executive functions in various contexts such as in neurology, development, aging and psychopathology (for review see Sweeney, Levy, & Harris, 2002). Specifically, successful performance of an antisaccade has been proposed to involve two executive cognitive processes: inhibition of the reflexive eye movement that normally is generated towards a novel visual target appearing in the periphery (so-called visually-guided or pro-saccade), and programming of a voluntary motor response towards its opposite direction in absence of any external visual guidance (Guitton, Buchtel, & Douglas, 1985; e.g. Hallett & Adams, 1980; for review see Munoz & Everling, 2004). However, recent theoretical accounts embed both these functions - inhibition of a reflexive behavior and programming of a volitional one - into a broader framework of executive control, proposing that the performance on the antisaccade probes the ability to pursue an internal task goal,

involving besides inhibitory capacity and voluntary saccade programming other cognitive functions such as working memory, and/or shifting of attentional focus (e.g. Mitchell, Macrae, & Gilchrist, 2002; Nieuwenhuis, Broerse, Nielen, & de Jong, 2004; Reuter & Kathmann, 2004).

Often, antisaccade performance is compared to performance of voluntary prosaccades (i.e. intended saccades towards the target, see Figure 3-1, panel A), in order to have a control condition for the sensory and motor requirements of antisaccade performance (Luna et al., 2001).

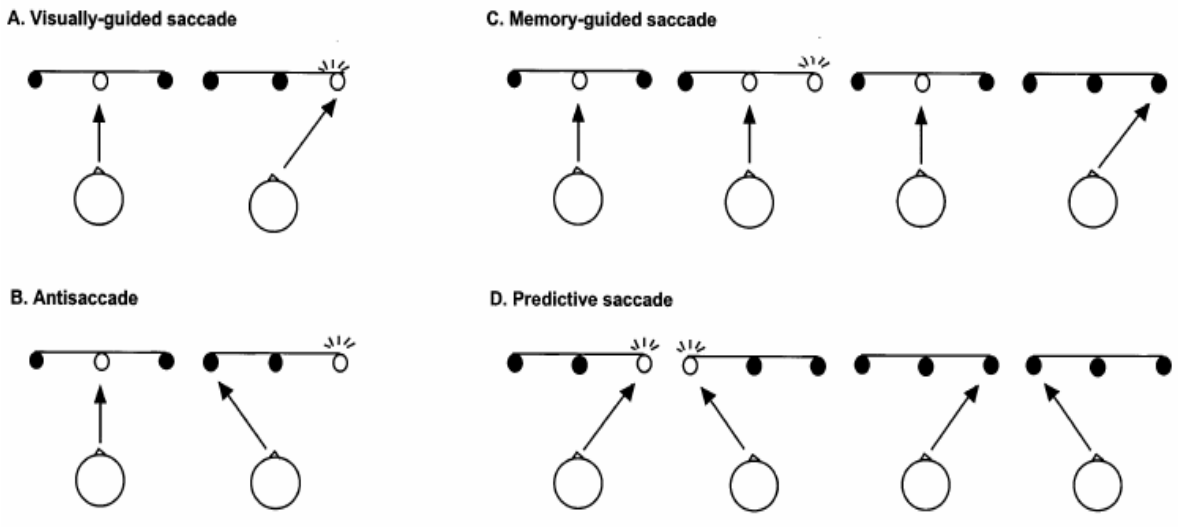

Figure 3-1: Different saccadic paradigms have been developed to examine different cognitive operations such as spatial attention, response inhibition, spatial working memory, and predictive and anticipatory behaviour. The core paradigms are: (A) Visually-guided paradigm: A visual stimulus is presented in a random sequence to the left of right of a central fixation point and subjects are instructed to respond with a rapid and accurate eye movement towards that stimulus. (B) Antisaccade paradigm: subjects are instructed to suppress the reflexive saccade that would normally be generated in response to a novel visual target, and to generate a volitional saccade to the opposite hemifield. (c) Memory-guided paradigm: Subjects are instructed to suppress the normal reflexive eye movement in response to a novel stimulus, and to delay the saccade until the offset of the central light. (D) A visible target steps between (two) fixed locations in a predictable temporal sequence, and subjects are instructed to repeat the sequence with their eye movements. From Broerse et al. (2001).

3.1.1 Antisaccade performance measures

AS task performance yields several global and dynamic measures that can be mapped onto specific neural substrates (see chapter 3.2), providing insights into the integrity of cognitive and neural mechanisms involved in the volitional control of behavior.

3.1.1.1 Global performance measures

Global measures of AS task performance include the proportion of correct antisaccades, proportion of erroneous prosaccades (also referred to as antisaccade direction errors), and the proportion of such errors being corrected. While the error rate has been proposed to index the integrity of inhibitory control processes, the rate of corrected errors has been suggested to reflect the ability to inter-

nally generate a voluntary response (for review see Broerse et al., 2001; Hutton & Ettinger, 2006; Munoz & Everling, 2004). Studies using large samples indicate mean error rates of about 20% on the antisaccade task in adults (Ettinger, Hejda, Flak, & Corr, 2005; Ettinger et al., 2003; Smyrnis et al., 2002; Tatler & Hutton, 2007).

3.1.1.2 Dynamic performance measures

Dynamic, temporal and spatial measures of AS task performance include the latency (the time between target onset and saccade initiation), duration, amplitude (the distance the eye travels during a saccade in degrees visual angle), and peak velocity of correct antisaccades, of antisaccade direction errors, and of corrected direction errors (for review see Broerse et al., 2001; Fischer, 1999; Hutton & Ettinger, 2006). Put in relation to the eccentricity of a visual target, saccade amplitude is a measure of the spatial accuracy of an eye movement, also referred to as saccade gain, with gains above 1 indicating saccade hypermetria, and gains below 1 saccade hypometria.

Antisaccades generally have longer latencies (about 100-150 ms) than voluntary prosaccades, which have longer latencies than direction errors (Munoz & Everling, 2004; Olk & Kingstone, 2003) (see Figure 3-2). In addition, antisaccades are less accurate, have smaller amplitudes and slower peak velocities than prosaccades (Amador, Schlag-Rey, & Schlag, 1998; Hallett, 1978). The differences between antisaccade and prosaccades dynamic performance measures have been proposed to reflect their different cognitive demands and thus underlying neural substrates (see chapter 3.2).

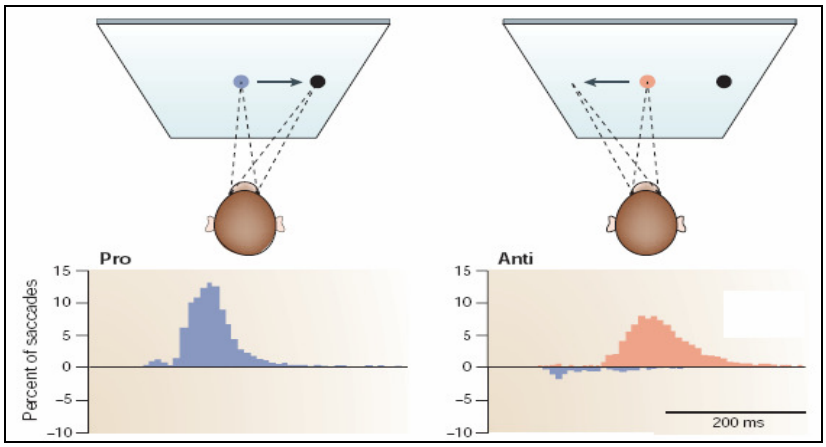

Figure 3-2: Antisaccades (right side panel, indicated by red color of the fixation cue) have longer saccade latencies than prosaccades (left side panel, indicated by blue color of the fixation cue). Prosaccades during antisaccade trials (direction errors) tend to have shorter latencies than volitional pro- and antisaccades. Adapted from Munoz and Everling (2004).

3.1.1.3 Indices related to antisaccade performance

Saccadic eye movements are just one type of event that can be observed while subjects are scanning the visual environment or performing a saccade task. Other events that are interspersed and/or go along with saccadic eye movements are for example the number of blinks, changes in the aperture of the pupillary lens (pupil dilation or constriction) or the number, location and duration of fixational eye movements. Eye movements are considered "fixations" if they do not exceed certain spatial and temporal limits. Commonly, an eye movement is defined as a fixation if the eye moves less than 0.5 degrees visual angle for at least 100ms (e.g. Karsh & Breitenbach, 1983; L. R. Young & Sheena, 1975).

Some of these eye movement measures have been shown to reflect endogenous factors influencing visual information processing. For example, higher cognitive demand and/or attentional engagement of an individual go along with increased number and duration of fixations and larger preparatory and more sustained pupil dilation, while arousal leads to a decrease in fixation duration but an increase in pupil dilation (for review see Beatty, 1982; Joos et al., 2003; Liversedge & Findlay, 2000; Steinhauer & Hakerem, 1992). Thus, although not directly measuring saccadic eye movements, the investigation of fixation parameters and changes in pupil diameter can inform about the cognitive and emotional state of an individual while performing the AS task.

3.2 Neural circuit underlying saccadic eye movements

Saccadic eye movements are among the best understood movements in terms of their underlying neural substrates (Leigh & Kennard, 2004; Ramat et al., 2007). Research using multiple technologies and methods in humans and non-human primates has identified several distinct populations of neurons (such as saccade-related and fixation-related neurons), in different brain regions (from brainstem to the cerebral cortex), that code for initiation and course of specific types of saccadic eye movements, respectively the ability to hold the eye still between them.

A central node in the neural system controlling visual fixation and saccadic eye movements is the superior colliculus (SC) of the midbrain (Scudder, Kaneko, & Fuchs, 2002) (see Figure 3-3). The SC receives and integrates input from several neural structures a) involved in the proximate processing of visual information such as the retina and the visual cortex, and b) involved in the programming of visual or goal-related behavior such as the parietal eye fields PEF (an area within the posterior parietal cortex PPC), the frontal eye fields FEF (an area anterior of the motor cortex), the supplementary eye fields SEF (an area in the dorsomedial PFC that may be considered an extension of the supplementary motor area SMA), the DLPFC, the basal ganglia, and the cerebellum. Saccades are triggered, if activity within saccade neurons in the SC - or upstream cortical eye fields projecting to the SC such as the FEF and PEF- reaches a certain saccade initiation threshold that is idiosyncratic for each neuron (Dorris & Munoz, 1998; Dorris, Pare, & Munoz, 1997; Everling, Dorris, Klein, & Munoz, 1999; Everling & Munoz, 2000; Gold & Shadlen, 2000; Hanes & Schall, 1996; Pare & Hanes, 2003), leading to

release of tonic inhibition and generation of a saccadic pulse command in a brainstem saccade generation network which innervates the six extraocular muscles of the eye. Alternatively, a saccade may be generated bypassing the SC by direct input from cortical areas such as the FEF and SEF to the brainstem saccade generating network. For more detail on the neural system involved in saccade generation based on primate electrophysiological studies, see reviews by Leigh and Kennard (2004) or Munoz and Everling (2004).

With increasing complexity of a saccadic eye movement in terms of its spatial and temporal characteristics, more upstream neural structures are involved in its generation (see Figure 3-3). For example, primate electrophysiological, and human imaging, transcranial magnetic stimulation (TMS) and lesion studies indicate that visually-guided and express saccades mainly recruit the SC, occipital cortex and PPC, while voluntary saccades additionally involve the FEF, and complex voluntary saccades such as antisaccades in addition to the PPC and FEF (where activity levels are enhanced as compared to visually-guided saccades), the DLPFC, SEF, SMA, the pre-SMA, ACC, basal ganglia, and thalamus (Broerse et al., 2001; for review see Gaymard, Ploner, Rivaud, Vermersch, & Pierrot-Deseilligny, 1998; Hutton & Ettinger, 2006; Leigh & Kennard, 2004; Munoz & Everling, 2004; Pierrot-Deseilligny, Ploner, Muri, Gaymard, & Rivaud-Pechoux, 2002).

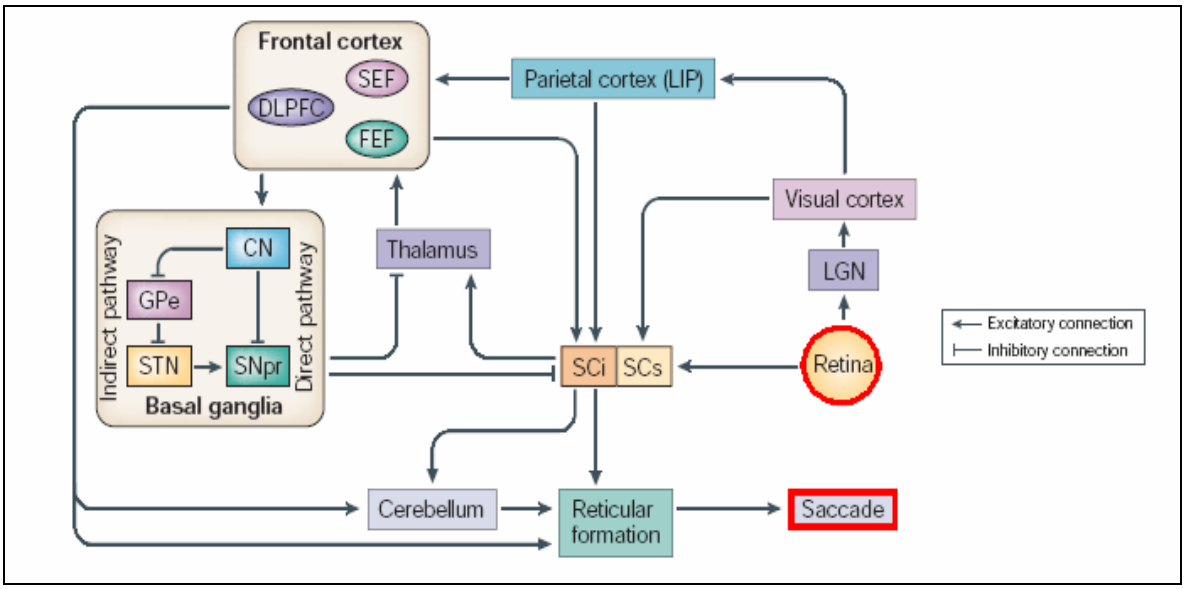

Figure 3-3: Visual input to the eye movement and visual fixation system is transmitted from the retina to the superficial layers of the superior colliculus (SCs) in the midbrain (retinotectal pathway), and via the thalamus (lateral geniculate nucleus LGN) to the primary visual cortex (retino-geniculo-cortical pathway). In order to influence motor behavior, the information is further transmitted from the visual cortex to the parietal eye fields (PEF, in primates referred to as intraparietal area LIP), which in turn project to the intermediate layers of the superior colliculus (SCi). The SC is a vital node in the premotor eye movement circuit where cortical and subcortical signals converge and are integrated. It provides the necessary input to the saccade premotor circuit so that a saccade is initiated or suppressed. In addition, the PEF projects to frontal oculomotor areas, including the frontal eye fields (FEF), supplementary eye fields (SEF), and the dorsolateral prefrontal cortex (DLPFC). All of these frontal cortical areas project to the SC, and the FEF and SEF in addition project directly to the reticular formation in the brainstem. Moreover, frontal cortical oculomotor areas project to the Caudate Nucleus (CN) of the basal ganglia. The CN projects either directly to the Substantia Nigra pars reticulata (SNpr), which leads to a disinhibition (i.e. activation) of the SCi, or indirectly through the external segment of the Globus Pallidus (GPe) and the subthalamic nucleus (STN), which leads to inhibition of the SCi. From Munoz and Everling (2004).

3.2.1 Neural correlates of antisaccade performance measures

Different antisaccade parameters have been mapped onto specific neural substrates and circuits. Below, antisaccade performance parameters informing about the functional state of the neural circuit underlying its generation will be outlined in more detail. For more reviews on the neural underpinnings of antisaccades, see Munoz and Everling (2004) or Everling and Fischer (1998).

3.2.1.1 Antisaccade error rate

As mentioned in chapter 3.1, correct antisaccade performance has been proposed to require a) the canceling or inhibition of the reflexive saccade triggered by target appearance, to allow time for b) a voluntary saccade to be programmed and initiated towards the opposite side of the target (Hallett & Adams, 1980; for review see Munoz & Everling, 2004). According to this view, antisaccade errors occur if the neural cancellation process is too slow or too weak.

Neurophysiological evidence supports the proposition of an active cancellation process taking place before antisaccade generation. Specifically, saccade neurons in the FEF and SC show decreased activity and fixation-neurons in the FEF and SC enhanced activity before correct antisaccades as compared to correct prosaccades (Everling et al., 1999; Everling & Munoz, 2000; Munoz & Everling, 2004). In contrast, high pre-target activity in the SC saccade neurons goes along with increased error rates on antisaccade trials (Everling, Dorris, & Munoz, 1998).

The origin of the inhibitory influence on the FEF and SC on the other hand is still somewhat unclear. Brain regions that have been implicated are the DLPFC, SEF, and the basal ganglia (for review see Munoz & Everling, 2004). For example, enhanced neural activity has been demonstrated in single-neuron monkey studies in DLPFC neurons before performance of correct antisaccades (Funahashi, Chafee, & Goldman-Rakic, 1993), and enhanced neural activity in the SEF before performance of correct antisaccades as compared to correct prosaccades (Amador, Schlag-Rey, & Schlag, 2004; Schlag-Rey, Amador, Sanchez, & Schlag, 1997) (see also chapter 3.2.1.2). Likewise, imaging studies have shown increased activity in prefrontal cortex regions such as the DLPFC, SEF, and ACC before execution of correct antisaccades as compared to prosaccades, or as compared to antisaccade direction errors (Connolly, Goodale, Goltz, & Munoz, 2005; Curtis & D'Esposito, 2003; DeSouza, Menon, & Everling, 2003; Ford, Goltz, Brown, & Everling, 2005). In addition, clinical, lesion and TMS studies demonstrate increased error rates on the antisaccade task after DLPFC and basal ganglia impairment. For example, TMS over the DLPFC 100ms before target onset significantly increases antisaccade error rate (Nyffeler et al., 2007), and patients with discrete lesions affecting the DLPFC, clinical populations with impairment of the DLPFC respectively the basal ganglia such as patients with schizophrenia, Huntington's and Parkinson's disease, and patients with lesion of the ventrolateral PFC and ACC have been reported to show an increased proportion of direction errors on the antisaccade task (for review see Gaymard et al., 1998; Milea, Lobel, Lehericy, Pierrot-Deseilligny,

& Berthoz, 2005; Pierrot-Deseilligny et al., 2002; Sweeney et al., 2002). In contrast, lesions of the PEF, FEF, or SEF/SMA have not been shown to influence antisaccade error rate (e.g. Gaymard, Lynch, Ploner, Condy, & Rivaud-Pechoux, 2003; Gaymard, Pierrot-Deseilligny, & Rivaud, 1990; Husain, Parton, Hodgson, Mort, & Rees, 2003; Rivaud, Muri, Gaymard, Vermersch, & Pierrot-Deseilligny, 1994).

However, enhanced activity in prefrontal brain regions may also reflect the programming and promotion of the correct antisaccade by these areas. Some researchers even have proposed that there might be no (active) cancellation process during antisaccade trials, but instead that distinct neural networks in the DLPFC, SEF, FEF or PEF simultaneously program a visually-guided prosaccade and an internally-guided antisaccade, and that the strength of activation first reaching saccade initiation threshold determines which movement will be executed, the other one being cancelled on the go (Amador et al., 2004; Massen, 2004; Mokler & Fischer, 1999; e.g. Schlag-Rey et al., 1997). According to this view, increased error rates in the antisaccade task may result if the programming of the antisaccade is slower than that of the visually-guided prosaccade, possibly because of a slower increase in activity towards the saccade initiation threshold in neurons coding for the antisaccade (Hutton & Ettinger, 2006). Whatever the specific executive role of the PFC in antisaccade programming is, i.e. inhibition of a reflexive prosaccade and/or promotion of the voluntary antisaccade, PFC function certainly plays a crucial role in determining antisaccade error rate.

3.2.1.2 Latency

Saccades are triggered if saccade neurons in the SC or FEF reach a particular activity level that is idiosyncratic for each neuron (see also chapter 3.2). Saccade latency thus has been proposed to reflect the pre-target activity of neurons capable of triggering a saccade, respectively the rate of rise in their post-target activity (for review see Munoz & Everling, 2004).

For voluntary saccades, movement-related activity within the FEF seems to be essential in determining latency. For example, patients with FEF lesions make correct antisaccades at increased latency (Braun, Weber, Mergner, & Schulte-Monting, 1992; Rivaud et al., 1994). Moreover, TMS applied over the FEF influences the latency of contralateral, memory-guided saccades (Pierrot-Deseilligny et al., 2002; Wipfli et al., 2001). Finally, monkey single-neuron and human imaging studies have shown an inverse correlation between FEF preparatory activity and latency of contralateral voluntary saccades, but no such relationship for SEF or PEF pre-target activity (Connolly et al., 2005; Everling & Munoz, 2000). In contrast, visually-guided saccades seem to depend on the PEF, respectively SC function. For example, after PEF but not FEF or SEF lesions, latency of visually triggered saccades is significantly increased, and SC damage reduces the ability to generate express saccades, i.e. visually-guided saccades with very short latencies (Pierrot-Deseilligny, Rivaud, Gaymard, & Agid, 1991).

The origin of the variability of growth of activity in the FEF is not known. It could for example be accounted for by the state of neuromodulatory systems (e.g. Aston-Jones, Rajkowski, Kubiak, & Alexinsky, 1994), and/or by upstream eye movement areas involved in executive functions such as the DLPFC or SEF. Recently, Stuphorn and Schall (2006) could demonstrate a modulatory influence of the SEF on saccade performance that depended on task goal. Specifically, subthreshold intracortical microstimulation of the monkey SEF lead to better performance on a "stop signal" eye movement task by delaying saccade initiation (i.e. increasing latency). In contrast, on a visually-guided control task, where no stop signal occurred and no executive function was necessary, SEF microstimulation decreased saccade latency. Similar findings of a modulatory influence of the SEF on eye movements have been reported by Missal and Heinen (2001), who showed increased velocity and decreased latency of anticipatory smooth pursuit eye movements after microstimulation of the SEF. Such an executive function of the SEF on voluntary eye movements is consistent with enhanced SEF activity before correct antisaccades than prosaccades in monkey studies (Amador et al., 2004; Schlag-Rey et al., 1997) (see chapter 3.2 above), in imaging studies (Ford et al., 2005; e.g. O'Driscoll et al., 1995; Sweeney et al., 1996), and ERP recordings (Everling, Krappmann, Spantekow, & Flohr, 1997; Everling, Spantekow, Krappmann, & Flohr, 1998).

3.2.1.3 Metric performance measures

From a neural perspective, the coding of saccade metrics requires sensorimotor, as well as spatiotemporal transformations. Specifically, the location of a target of interest in visual, auditory, and/or somatosensory space (the saccade goal) needs to be mapped onto a population of neurons with topographically arranged motor fields such that activity in specific neurons out of this population codes for a movement towards this specific location. The spatially coded signal subsequently needs to be transformed into a motor command that is related temporally to the saccade, i.e. informing the eye muscles when to start and when to stop contracting in what intensity to move the fovea to this location of interest.

A large body of evidence points towards an important role of the PPC in sensorimotor transformation, respectively the mapping of saccade targets onto movement-related neurons (for review see Andersen, 1995; Munoz & Everling, 2004). For example, many neurons in the intraparietal area LIP of the monkey have overlapping visual receptive and motor fields, i.e. these neurons become active if a visual target falls in their receptive field, and/or if a movement is planned towards a location in this area, with particularly strong activity if both are true, i.e. when the stimulus signals the saccade target, as is the case with visually-guided saccades (e.g. Zhang & Barash, 2000, 2004). In addition, when the visual stimulus and saccade goal do not match, as is the case with antisaccades, neurons in the area LIP respectively its human analogue show a shift in population activity from neurons encoding the visual target to those encoding the saccade goal (Zhang & Barash, 2000), respectively from the hemisphere contralateral to the stimulus to that contralateral to the target goal (Everling, Dorris et al.,

1998; Medendorp, Goltz, & Vilis, 2005; Moon et al., 2007). Additional support for a role of PPC in coding for the saccade target comes from TMS and lesion studies showing saccadic dysmetria with PPC dysfunction (Duhamel, Goldberg, Fitzgibbon, Sirigu, & Grafman, 1992; Nyffeler et al., 2005; Pierrot-Deseilligny et al., 2002; Pierrot-Deseilligny et al., 1991).

The spatiotemporal transformation of the neural signal coding for saccade amplitude is supposed to take place in the SC and/or cerebellum, both of which project to the brainstem saccade generating circuit. Yet, as with sensorimotor transformation, the precise neural mechanisms underlying spatiotemporal transformation are still being debated (Optican, 2005; for different models and review see Scudder et al., 2002; Sparks, 2002). So far, the available evidence points towards a role of the SC in initiating the saccadic movement, with the location of SC neurons activated providing initial information on the direction and amplitude of the saccade (i.e. spatial coding), and the strength of the activating pulse coding for its initial velocity, while the cerebellum is involved in adapting the course of the saccade to land on its supposed goal by adjusting velocity and providing the accurate stop signal (and thus defining saccade amplitude by temporal means), using feedback about the parameters of the ongoing saccade (e.g. Optican, 2005; Quaia, Lefevre, & Optican, 1999). In the brainstem, the firing pattern of saccade-generation neurons is related temporally to the dynamics of a saccadic eye movement. For example, the duration of activity of these neurons is related to the duration of the saccade, their firing rate to its peak velocity, and the overall number of spikes to its amplitude (King, Fuchs, & Magnin, 1981; for review see Leigh & Kennard, 2004).

Finally, although the coding of saccade metrics does not require frontal cortical regions, the latter may exert a modulatory influence. For example, TMS over the DLPFC in normal subjects, and lesions of the DLPFC, SEF, and FEF have been reported to impair the accuracy and peak velocity of voluntary saccades (Dias & Segraves, 1999; Fukushima, Fukushima, Miyasaka, & Yamashita, 1994; Husain et al., 2003; Oyachi & Ohtsuka, 1995; Sommer & Tehovnik, 1997).

3.2.1.4 Fixation duration

During natural viewing, saccades follow fixations and vice versa, i.e. there is an interplay between saccades that drive the eye to fixate points of interest and select new possible targets for future saccades. Accordingly, the neural substrates coding for movement and stopping of the eye are closely intertwined: Most areas involved in saccadic eye movements such as the SEF, FEF, PPC, SC, and brainstem contain neurons that are active shortly before and during a saccade and neurons that are active during fixational eye movements (Everling et al., 1999; Munoz & Everling, 2004; Munoz & Wurtz, 1993). These so-called fixation neurons have visual receptive fields that cover the fovea, i.e. the part of the retina with highest visual acuity. Activity of fixation neurons helps the eye to remain “locked” on an object of interest in the environment: Blockade of fixation neurons in the SC for example leads to the generation of saccades to every new stimulus that appears in the environment (Munoz & Wurtz, 1993).

3.2.1.5 Pupil diameter

The so far presented measures about the movement or the holding of the eye are ultimately under the control of the voluntary motor system. Pupil diameter in contrast is modulated by activity of the autonomous nervous system, with complementary functions of its parasympathetic and sympathetic components: While activation of the sympathetic pathway stimulates the radial dilator muscles of the pupil, causing enlargement of the pupillary aperture, activation of the parasympathetic efferent to the pupil leads to contraction of the sphincter muscles, a band of muscles arranged in circular orientation around the pupillary margin, causing constriction of the pupillary aperture (for review see Schandry, 1998). Evidence indicates that both autonomous pathways are involved in pupil dilation observed under cognitive and emotional demand (see chapter 3.1.1.3), however along different timelines, and under differing circumstances. Specifically, under light conditions, high cognitive demand, and/or about 600 to 900 ms after stimulus onset, pupil dilation is more strongly determined by parasympathetic inhibition, while after about 1200 ms and in darkness, activation of the sympathetic pathway may cause the pupil diameter to enlarge (e.g. Steinhauer, Siegle, Condray, & Pless, 2004). Both, modulation of the parasympathetic pathway as well as the sympathetic pathway are influenced by corticolimbic inputs (for review see Steinhauer & Hakerem, 1992). For example, stimulation of the amygdala (Koikegami & Yoshida, 1953) as well as increase in DLPFC activity (Siegle, Steinhauer, Stenger, Konecky, & Carter, 2003) leads to increase in pupil dilation.

3.3 Saccadic eye movements in development

Different antisaccade performance parameters mature along different time lines during childhood and adolescence. For example, children below the age of 8 years have great difficulty suppressing reflexive prosaccades towards the target, with two- to three times higher antisaccade error rates than adults (Fischer, Biscaldi et al., 1997; C. Klein & Foerster, 2001; Munoz, Broughton, Goldring, & Armstrong, 1998). Yet, most children immediately correct the direction errors they have committed, indicating that they understand the task and are able generate an antisaccade per se (Munoz et al., 1998). Antisaccade error rates gradually decrease during adolescence to reach adult level at about 18 years of age (Fischer, Biscaldi et al., 1997; Fukushima, Hatta, & Fukushima, 2000; Kramer, de Sather, & Cassavaugh, 2005; Luna et al., 2001; Munoz et al., 1998). In addition, latency of correct antisaccades, of corrective gazes and of prosaccades becomes less variable and decreases overall during adolescence, albeit at slightly different timescales: While prosaccade latency reaches adult levels at around late childhood/early adolescence, antisaccade latency reaches adult levels later at around middle adolescence and shows a greater overall change than prosaccade latency (Fischer, Biscaldi et al., 1997; Fukushima et al., 2000; Irving, Steinbach, Lillakas, Babu, & Hutchings, 2006; C. Klein, 2001; Kramer et al., 2005; Munoz et al., 1998) (see also Figure 3-4). Finally, in contrast to antisaccade error rate and latency, saccade metrics such as peak velocity and amplitude as well as other eye movement parameters such as pupil dilation and fixation duration reach adult patterns well before puberty onset

(Abel, Troost, & Dell'Osso, 1983; Fukushima et al., 2000; Irving et al., 2006; Karatekin, 2004; Luna et al., 2001; Munoz et al., 1998). One study (Irving et al., 2006) showed that peak velocity increases during childhood to reach its maximum at age 14, and steadily declines thereafter.

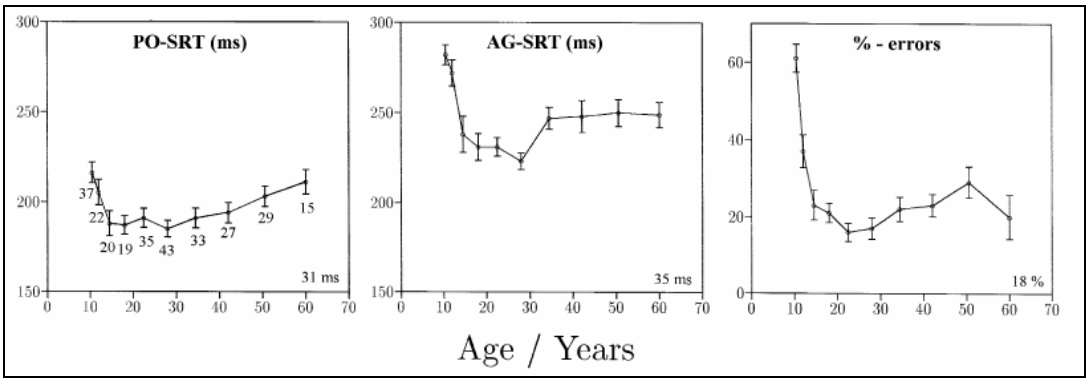

Figure 3-4: Age related modulation of saccade parameters in a prosaccade-overlap (i.e. fixation point remains illuminated during target appearance) and antisaccade-gap (i.e. fixation point is turned off before target appearance) paradigm. The number of subjects is given in the left panel. SRT = saccadic reaction time; PO = prosaccade-overlap; AG = antisaccade-gap; %-errors = percent direction errors in the AG task. From Fischer et al. (1997).

The different time lines along which the different antisaccade performance parameters develop have been proposed to reflect the maturational course of their underlying neural substrates. For example, increased antisaccade error rates and longer, respectively more variable, pro- and antisaccade latency in young subjects relative to adults have been suggested to reflect a weak voluntary saccade initiation system (Fischer, Biscaldi et al., 1997), difficulty in controlling visual attention (Munoz et al., 1998), or inability to maintain multiple top-down sets in working memory (e.g. inhibit an eye movement to a salient stimulus and move the eyes in the opposite direction) (Eenshuistra, Ridderinkhof, Weidema, & van der Molen, 2007; Kramer et al., 2005), as a function of immature prefrontal executive control (e.g. Fukushima et al., 2000; Munoz et al., 1998). Indeed, the first fMRI study comparing neural activity during antisaccade performance between adolescents and adults indicated that although adolescents and adults recruit largely the same brain regions during antisaccade performance, adolescents more strongly recruit prefrontal regions such as the DLPFC and inferior FEF, and adults more strongly posterior and subcortical brain sites such as the PPC, thalamus, cerebellum, and SC (Luna et al., 2001). In addition, the earlier maturation of antisaccade latency as compared to antisaccade error rates has been proposed to indicate that these parameters are subserved by different PFC substrates that mature along different timelines (C. Klein, 2001; C. Klein & Foerster, 2001). Finally, the earlier maturation of saccade metrics has been suggested by the different authors to indicate earlier development of sensorimotor neural processing circuits (Luna et al., 2001) respectively the saccade generation network in the cerebellum and brainstem (Fukushima et al., 2000; Irving et al., 2006; Munoz et al., 1998).

3.4 Saccadic eye movements in mood and anxiety disorders

Antisaccades recruit an extensive neural circuit parts of which have been implicated in the pathophysiology of several psychiatric disorders such as schizophrenia, and mood- and anxiety disorders. Thus, investigation of AS task performance in psychiatric patients can not only provide quantifiable information about cognitive (dys-) functions in these patient populations, but also allows drawing conclusions about the functional state of associated neural circuits.

However, while a wealth of research has looked at AS task performance in patients with schizophrenia (Hutton & Ettinger, 2006; for review see Sweeney et al., 2002), surprisingly few studies have investigated AS task performance in mood and anxiety disorders (for review see Broerse et al., 2001; Sweeney et al., 2002). In addition, most studies investigating AS task performance in mood and anxiety disorders have reported inconsistent results. According to a review by Sweeney et al. (2002), performance differences might be evident only with large samples of mildly affected individuals, or with severely depressed, unmedicated patients. Prior to the data presented in this thesis (Jazbec et al., 2005), no study has investigated AS task performance in depressed and anxious adolescents. However, several studies have been done with children and adolescents with ADHD (Goldberg et al., 2002) and autism (e.g. C. Klein, Raschke, & Brandenbusch, 2003; Munoz, Armstrong, Hampton, & Moore, 2003), indicating that the AS task may be useful for investigating brain dysmaturation in multiple neuropsychiatric disorders (Luna & Sweeney, 2004).

In contrast to the AS task, other eye movement parameters such as fixation duration and pupil diameter have been more extensively studied in adult and child mood and anxiety disorders, mostly as an index of attentional biases or cognitive demand. In terms of fixation duration, Caseras et al. (2007) for example reported that dysphoric individuals engage longer in processing of negative information (indexed as longer gaze duration on pictures showing negative scenes such as sadness and loss), however not differing from controls in initial attention orientation (indexed as latency of the first fixation) (for similar results see Eizenman et al., 2003). In contrast, anxious individuals have been reported to exhibit biases in initial orienting, but not in the maintenance of gaze on threat cues (Garner, Mogg, & Bradley, 2006; e.g. Mogg, Millar, & Bradley, 2000). To my knowledge, no study has looked at fixation duration in anxious or depressed adolescents.

In terms of pupil dilation, Siegle et al. (2001) have shown that depressed patients engage longer than controls in the processing of emotional (positive and negative) information as indexed by longer sustained pupil dilation. In contrast, depressed individuals engage less (i.e. have smaller sustained pupil dilation) than controls when processing non-emotional information, such as during performance of the Stroop color-naming task (Siegle, Steinhauer, & Thase, 2004). Interestingly, a recent study by Silk et al. (2007) reported that depressed adolescents in contrast to depressed adults show decreased sustained pupil dilation to negative information, which was associated with a decrease in positive affect and increase in negative affect in the natural environment. In anxiety, there is evidence for increased pupil dilation under anticipation of threats, and decreased pupillary constriction to light (e.g. Bitsios, Szabadi, & Bradshaw, 2004).

3.5 Saccadic eye movements and reward processing

Incentives influence saccade performance parameters. For example, in non-human primates, saccades to a rewarded location are initiated earlier, have faster peak velocities and are more accurate (Kawagoe, Takikawa, & Hikosaka, 1998; Kobayashi, Lauwereyns, Koizumi, Sakagami, & Hikosaka, 2002; Takikawa, Kawagoe, Itoh, Nakahara, & Hikosaka, 2002); in humans, the number of correct antisaccades increases with incentives in adults (Duka & Lupp, 1997). Based on this influence of incentives on saccadic eye movements, it has been proposed that “saccadic eye movements can be a suitable behavioral measure for studying reinforcement learning and motivation” (Takikawa, Kawagoe, Itoh et al., 2002, pg. 284).

The influence of reward on saccadic eye movements is proposed to be mediated through its basal ganglia pathway (Hikosaka, Takikawa, & Kawagoe, 2000), and/or the prefrontal eye movement areas such as the DLPFC, SEF and ACC (see also Figure 3-3). Simplified, the basal ganglia pathway exerts tonic inhibition on saccade-related neurons in the SC. This inhibition can be released by PFC input into the basal ganglia, leading to saccade generation by the SC. Neurons in the basal ganglia pathway receive dopaminergic input from the midbrain, which may inform about the significance of events (see chapter 2.2.1.1), and have been shown to substantially modulate their firing patterns in response to incentives (Lauwereyns, Takikawa et al., 2002; Lauwereyns, Watanabe, Coe, & Hikosaka, 2002). Also the SEF and ACC receive dopaminergic input from the VTA (Gaspar, Stepniewska, & Kaas, 1992), and indeed both have different subpopulations of neurons that show a response pattern that varies depending on the outcome of a saccade (i.e. obtain reward, commit an error) (Niki & Watanabe, 1976, 1979; Stuphorn, Taylor, & Schall, 2000). Finally, pharmacological inactivation of DLPFC with D1 dopamine antagonists impairs the accuracy of contralateral memory guided saccades in monkeys (Sawaguchi & Goldman-Rakic, 1994).

3.6 Synopsis chapter 3

The antisaccade (AS) task paradigm is uniquely well suited to study the influence of incentives on executive cognitive control during normative development and in psychiatric neurodevelopmental disorders such as adolescent mood and anxiety disorders, for several reasons:

1. AS task performance probes different executive cognitive processes such as response inhibition and attention allocation. However, in contrast to traditional neuropsychological paper-and-pencil tests, the AS task is simple, requiring only minimal verbal skills, and has inputs that can be easily manipulated and outputs that can be measured with precision, providing besides global performance measures quantitative information about the temporal dynamics of task responses (see chapter 3.1).
2. The neural mechanisms engaged during performance of the AS task have been largely delineated in non-human primates, providing a superb tool for translational work, and in humans by means of functional imaging, TMS and lesion studies (see chapter 3.2).

3. The developmental trajectories of the AS task paradigm have been well characterized in humans, allowing a baseline against which to compare performance of pediatric patients (see chapter 3.3). In addition, the AS task is non-invasive, and can be easily combined with fMRI research, an advantage in the study of pediatric populations.

4. Many psychiatric disorders such as mood and anxiety disorders are associated with abnormalities in brain structures engaged during performance of the AS task. Performance on the AS task thus can inform about the functional status of associated brain systems in patients with mood and anxiety disorders, respectively about the dysmaturation of these brain systems in pediatric patients (see chapter 3.4).

5. Finally, studies of reward processes using saccadic eye movements have already been conducted in non-human primates and in human adults, providing a basis for forming hypotheses and interpreting findings.

4. Summary and hypotheses

Behaviorally, adolescence is a time period of heightened “storm and stress”, characterized by an increase in impulsive behaviors, emotional turmoil, and an increase in prevalence of psychiatric disorders such as mood and anxiety disorders with their high continuity into adulthood and severe implications for later psychosocial functioning (see chapter 1). Neurally, adolescence is characterized by profound structural and functional reorganization of brain systems involved in the regulatory top-down control of affective states and behaviors (see chapter 2.1). Developmental neuroscientists have tried to link the behavioral and neural characteristics of the adolescent age span, proposing that the slow maturation of regulatory brain mechanisms during adolescence leads to a temporary time span in which impulses and affects – intensified by the surge of hormones at puberty - exert disproportional influence on adolescent behavior, leading to externalizing (see chapter 2.2) and/or internalizing (see chapter 2.3) adjustment problems, and in some instances in conjunction with genetic predispositions and/or environmental stressors to the development of mood and anxiety disorders and increased risk for suffering from these disorders in adulthood. Thus, research investigating adolescent brain maturation and cognitive regulatory control may not only help our understanding of adolescent normative behavioral propensities, but also advance our knowledge of pathogenic factors involved in the development of adult mood and anxiety disorders, eventually leading to the design of earlier, and more focused treatment strategies (Cicchetti & Posner, 2005; R. J. Davidson et al., 2002).

To further advance the developmental cognitive neuroscience approach on the research of normative adolescence and adolescent mood and anxiety disorders, dissociable behavioral components need to be identified that show peculiarities in these populations and that can be mapped onto specific neural correlates (Ernst et al., 2006; Forbes & Dahl, 2005; Hasler, Drevets, Manji, & Charney, 2004; Pine, 2007). One such promising approach is the study of the influence of incentives on cognitive control processes during adolescence (see synopsis chapter 2). However, prior to the data presented in this thesis (Jazbec et al., 2005), no research employing basic neuroscience measures has directly examined the association between adolescent affective disorders and reward-related information processing (see chapter 2.2.3), and neuroscience-based research addressing reward-processing in healthy adolescents are predominantly based on fMRI studies which to date have reported inconsistent results (for review see chapter 2.2.2).

To fill this gap, a behavioral task was developed to probe the influence of incentives (obtain reward, avoid punishment) on cognitive regulatory control (attention allocation, response inhibition) in pediatric populations, employing basic neuroscience measures. Saccadic eye movements offer themselves as a complementary neuroscience-based investigational means to fMRI studies, since they can be integrated in paradigms testing executive cognitive processes, are sensitive to incentive manipulation, and finally provide quantitative and easily measurable information on the temporal characteristics of information processing which can be mapped onto well delineated neural circuits (see chapter 3).

Thus, a saccadic eye movement task, the Reward Saccade Task (RST) was developed that investigated saccadic eye movements of differing cognitive demand (i.e. antisaccades versus prosaccades) under different incentive conditions (reward condition: obtain monetary gain with correct performance, punishment condition: monetary loss with incorrect performance, neutral condition: no monetary consequence of task performance), in development (comparison of healthy adolescents and adults) and in mood and anxiety disorders (comparison of healthy adolescents and adolescents with a mood and/or anxiety disorder). The effect of incentives was measured at two stages of the task, during task performance (work to obtain reward), and during outcome notification (processing of outcome). The following hypotheses were addressed:

Developmental focus

1. **Task performance improves with age**: Adults will perform better than adolescents under high cognitive demand. Specifically, in line with previous research on saccadic eye movements (see chapter 3.3) it is hypothesized that adults will have lower antisaccade error rates and initiate correct antisaccades faster in the RST than adolescents. After an antisaccade direction error, adults will be able to more quickly shift attention to initiate a corrective saccade than adolescents. In contrast, saccade measures that are independent of prefrontal function such as saccade duration and amplitude will not differ between age groups.
2. **Incentives improve task performance**: Rewards are stimuli which an organism puts forth effort to obtain, and punishments are stimuli which he puts effort to avoid (see chapter 2.2.1). Primate studies have shown a facilitatory effect of incentives on saccade performance (see chapter 3.5). Thus, it is hypothesized that there will be better performance on the RST across groups on trials with incentives than on neutral trials; this will be evident in all measures of task performance, on global (better accuracy) as well as dynamic performance measures (shorter saccade latency, faster saccade peak velocity).
3. **Adolescents will show stronger modulation of task performance by incentives than adults**:
    a. Adolescents have been reported to be more sensitive to rewards than adults (see chapter 2.2.2). It is thus hypothesized that adolescents will show stronger within-group modulation of task performance by incentives than adults.
    b. Findings from fMRI studies suggest that recruitment of cognitive control as a major function of the prefrontal cortex (for review see chapter 2.1.2) may normalize function of subcortical brain regions mediating affective states and impulses (e.g. Monk et al., 2008). Thus, it is hypothesized that the influence of incentives will be stronger for conditions of low cognitive control, i.e. it will be greater for correct prosaccades and antisaccade direction errors than antisaccades.
4. **Adolescents will be less affected by negative feedback than adults**. It has been proposed that adolescents are less sensitive to punishments than adults (see chapter 2.2.2). Processing of affective information is reflected in pupil diameter, pupil dilation and fixation duration (see chapter

3.2.1). Thus it is hypothesized that adolescents will have smaller changes in pupil diameter and/or in fixation duration between incentive and neutral trials as compared to adults.

Clinical focus

1. **Diagnostic state will not influence task performance**: Given that differences in (anti-) saccade performance between patients with depression and controls have only been reported for adults with severe depression (see chapter 3.4), it is hypothesized that adolescents with MDD and adolescents with anxiety will not differ from controls in antisaccade performance per se.
2. **Depressed and anxious adolescents will show different modulation by incentives than healthy adolescents**:
    a. *Depressed adolescents* have been proposed to suffer from anhedonia (see chapter 2.2.3), which can be operationalized as decreased effort to obtain positive outcomes, i.e. obtain rewards and avoid punishments (see chapters 2.2.1). In the RST, adolescents with MDD are thus hypothesized to show a weaker modulation (improvement) of task performance by incentives as compared to controls.
    b. *Anxious adolescents* have been reported to be hypersensitive to punishment and to exhibit an attentional bias for negative information (see chapter 2.2.3). During the RST, it is hypothesized that adolescents with anxiety will show an attentional bias for punishment trials as compared to neutral trials. This will specifically be reflected in better performance in patients with anxiety on punishment trials (i.e. better accuracy, earlier saccade latencies) as compared to neutral trials and as compared to controls.
3. **Depressed and anxious adolescents will respond differently to feedback than controls**:
    a. *Depressed adolescents* will be less responsive to positive outcomes than controls, as indexed by shorter fixation duration and smaller pupil dilation for positive feedback as compared to negative feedback and as compared to controls.
    b. *Anxious adolescents* will avoid negative information more strongly than controls, as indexed by shorter fixation duration and smaller pupil dilation during notification of negative feedback.

III. EMPIRICAL PART

5. Methods

5.1 Participants

90 subjects were included in this study, 30 healthy adults (18m/12f; 28.09 ± 5.84 years), 32 healthy adolescents (17m/15f; 13.70 ± 2.19 years), 16 adolescents with an anxiety disorder (10m/6f; 12.44 ± 1.96 years), and 12 adolescent with a primary diagnosis of MDD (5m/7f; 14.15 ± 2.27 years). Groups did not differ in the proportion of sex ($\chi^2_{df=3}$ = 1.567, p = 0.667), and the three adolescent groups did not differ significantly in age ($F_{1,57}$ = 2.62, p = 0.082). Comorbid disorders within the anxiety spectrum and/or with MDD were common (see Table 5-1). For example, of the 12 adolescents with primary MDD, one third had a secondary comorbid anxiety disorder.

Prior entering the study, all participants were tested for IQ with the Wechsler Abbreviated Scale of Intelligence (WASI, Wechsler, 1999). Groups did not differ in IQ (adults 116.5 ± 11.5; control adolescents 112.6 ± 13.1; anxious patients 112 ± 14.4, depressed adolescents 107.5 ± 18.0; $F_{3,71}$ = 1.15, p = 0.336). In addition, subjects were assessed through semi-structured psychiatric interviews, adolescents through the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS-PL, Kaufman et al., 1997), adults through the Structured Clinical Interview for DSM-IV (SCID, Spitzer, Williams, Gibbon, & First, 1992). Clinical evaluation was performed by experienced clinicians who each had demonstrated acceptable inter-rater reliability (kappa > 0.75, Cohen, 1960) for all relevant diagnoses. This interrater reliability was set by NIH intern standards. Reliability was ascertained based on scoring of videotaped interviews that senior investigators had performed.

Inclusion criteria for healthy subjects were age between 9 and 17 years for adolescents and between 18 and 40 years for adults. Exclusion criteria were 1) presence of acute or chronic medical problems, 2) pregnancy, 3) current or past psychiatric disorders or 4) mental retardation (IQ < 70). Inclusion criteria for patients were 1) age between 9 and 17 years; 2) a primary DSM-IV diagnosis of an anxiety or major depressive disorder by semi-structured diagnostic interview (K-SADS-PL, Kaufman et al., 1997); 3) elevated symptoms on the Child Depression Rating Scale (CDRS-R > 39, Poznanski et al., 1984) for participants with a primary diagnosis of major depressive disorder, and elevated symptoms on the Pediatric Anxiety Rating Scale score (PARS > 10, Walkup & Davies, 1999) for participants with an anxiety disorder. Exclusion criteria were 1) treatment with any psychotropic medications for one month (two months for fluoxetine); 2) acute or chronic medical problems; 3) severe trauma history, post-traumatic stress disorder (PTSD), mania, psychosis, pervasive developmental disorder, or attention-deficit/hyperactivity disorder (ADHD) that requires treatment; 4) mental retardation (IQ < 70).

Table 5-1: Summary of diagnoses per patient included in the study (N = 28). SepAD: Separation Anxiety Disorder; SoP: Social Phobia; GAD: Generalized Anxiety Disorder; AgPh: Agoraphobia; SpecPh: Specific Phobias; OCD: Obsessive Compulsive Disorder; MDD: Major Depressive Disorder; ADHD: Attention Deficit Hyperactivity Disorder, Opp: Oppositional Defiant Disorder, Tic: Tic Disorder.

VP#	SepAD	SoP	GAD	AgPh / SpecPh	OCD	MDD	ADHD	Opp	Tic
1	x	x							
2						x			
3		x	x			x	x		
4		x		x		x			
5		x				x	x	x	
6			x						
7	x	x	x	x					
8						x			
9	x	x							
10						x			
11			x						
12	x	x					x		
13	x		x						
14			x				x		
15	x		x	x			x	x	
16			x				x		
17						x			
18	x	x				x		x	
19		x							
20	x								
21						x			
22					x				
23	x		x						
24						x			
25						x			
26						x			x
27	x								
28		x							
All	10	10	8	3	1	12	6	3	1

Healthy adults and adolescents were recruited through advertisements, contacts with medical organizations and word of mouth, patients were recruited when they sought treatment for an acute mood and/or anxiety disorder. The Institutional Review Board of the National Institute of Mental Health approved this study. Adults and parents of adolescent participants gave written informed consent, adolescents written assent prior to participation, after the study was fully explained and all questions answered. Immediately following assessment and testing, all patients were provided treatment. Eye movement testing was only one part of this study, which consisted of three visits each lasting between 2 to 4 hours. During the first visit, the study was explained, subjects consented and assessed regarding their physical health, IQ and diagnostic status. During the second visit, different paper-and-pencil tests and computer tasks were performed, one of them the eye movement task presented here. During the third visit, one of the computer tasks performed during visit two was repeated in an fMRI environment. Results of one of these tasks investigating brain activation during risk-taking in healthy adolescents was published in 2005 (Ernst et al., 2005) (see also chapter 2.2.2.2).

5.2 Procedures

Prior to performing the eye movement task, all subjects filled out the Spielberger State-Trait Anxiety Inventory (STAI, Spielberger, 1983), adult subjects the Beck Depression Inventory (BDI, Beck, Ward, Mendelson, Mock, & Erbaugh, 1961) and adolescents the Children's Depression Inventory (Helsel & Matson, 1984; CDI, Kovacs, 1982) in order to obtain a measure of current anxiety and mood levels. Subjects were then thoroughly trained on the eye movement task with printouts of the different task scenarios, and again after being set up for eye movement recording. Thorough training was conducted in order to prevent learning effects during task performance, to accustom subjects to the eye movement recording apparatus and to check for quality of eye calibration. After completion of the task, subjects filled out a debriefing questionnaire (see Appendix I).

5.2.1 Reward Saccade Task

For the purpose of testing the influence of incentives on cognitive control, an eye movement task, the so called “Reward Saccade Task” RST, was developed in which eye movements of differing cognitive difficulty (i.e. prosaccades and antisaccades) were to be performed under three incentive conditions: potential monetary gain, potential monetary loss and no monetary incentive.

Each trial of the task was comprised of three periods that allowed for the separate examination of distinct components of reward-related information processing such as motivation to work for reward, or response to outcome: (1) Initial cue period (1250-1750 ms), which informed subjects about the valence (reward, punishment, or neutral) of the trial and type of eye movement required (prosaccade or antisaccade); (2) the target or performance period (1850 ms), which prompted subjects to perform the required saccadic eye movement; (3) and the feedback period (1000 ms), during which participants were informed on the accuracy of their response and monetary outcome (see Figure 5-1).

Cue Period: Each trial began with presentation of one of 6 differently shaped and colored cues displayed at the center of a black computer screen, subtending approximately 0.5º visual angle. The *shape* of the cue indicated the valence of the trial: a plus sign (“+”) signaled a $1.00 monetary gain for subsequent correct performance, or no gain for incorrect performance (reward condition); a minus sign (“-“) signaled a $1.00 monetary loss for subsequent incorrect performance, or no loss for correct performance (punishment condition); and a circle (“o”) signaled no monetary consequences irrespective of subsequent performance (neutral condition). The *color* of the cue indicated the type of eye movement required in response to the subsequent appearance of the target: White cues required performance of a prosaccade (i.e., an eye movement towards the target), and gray cues required performance of an antisaccade (i.e., an eye movement to the mirror position of the target).

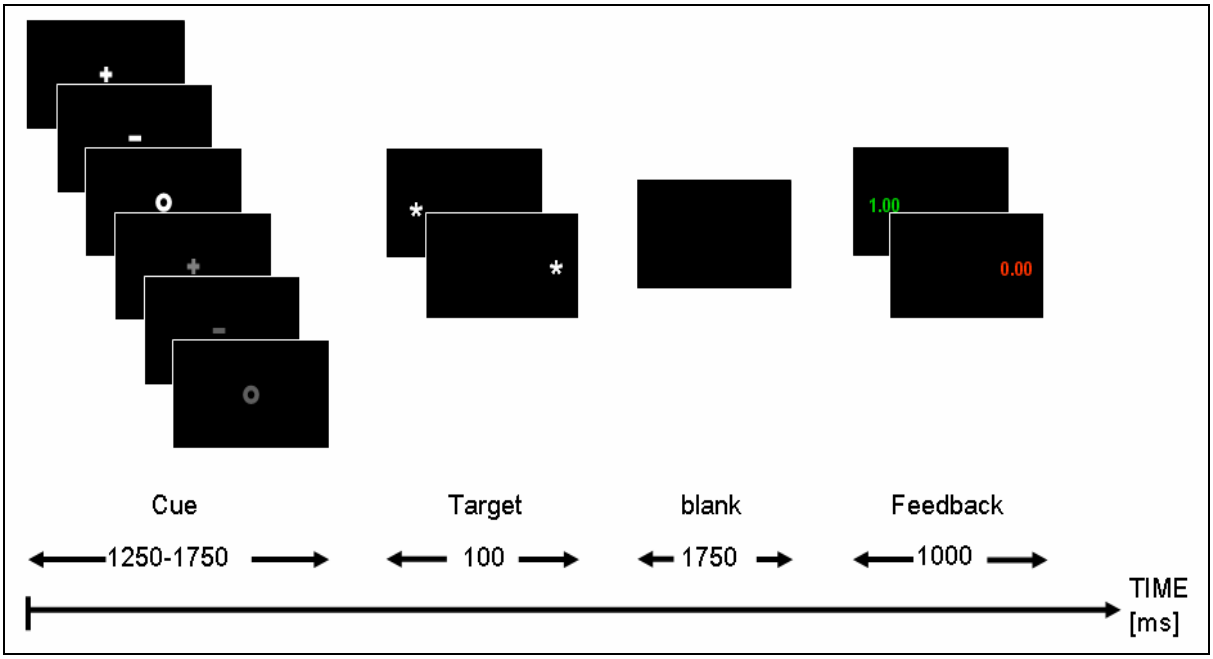

Figure 5-1: Reward Saccade Task paradigm: A cue (1250 to 1750 ms duration) is presented at the center of a black computer screen at onset of each trial. The cue indicates the type of trial (gray for antisaccade and white for prosaccade) and the incentive condition of the trial ('o' = neutral, '+' = gain, and '-' = loss). As the cue disappears, a target appears for a duration of 100ms on the right or left side of the screen. 1850 ms after target onset, accuracy feedback is provided for 1000ms duration. As the feedback disappears, the next trial starts with appearance of the cue.

Target Period: After a variable period of 1250-1750ms, the central cue was replaced by the target stimulus, a white asterix ("*") subtending 0.5º visual angle located approximately 6.15º eccentricity on the horizontal meridian either to the left or the right from the middle of the task screen and presented for a duration of 100ms. To succeed on a trial, subjects had to shift their gaze within 500ms after appearance of the target to the correct location, defined as an area of 60 pixels radius around the target in case of prosaccade trials or its mirror location in case of antisaccade trials, and to keep it there for at least 100ms (see Figure 5-2). Of note, criteria for performing well on the task differed from accuracy criteria employed for analysis (see chapter 5.3.2.1).

Feedback Period: After 1850ms duration, feedback appeared at the location where the subject was supposed to have gazed, i.e. at the location of the target in prosaccade trials, or at the mirror location of the target in antisaccade trials. It was presented in form of dollar amounts (+ $1.00, - $1.00, $0.00) subtending approximately 1.8º visual angle, printed in green font for a correct response and in red font for an incorrect response.

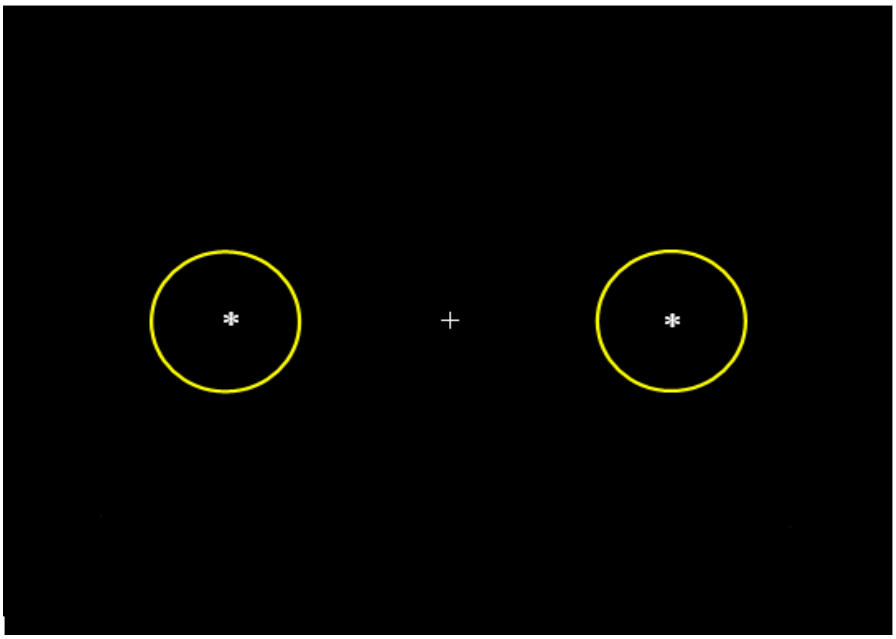

Figure 5-2: Accuracy definition for task performance: To succeed on a trial, subjects had to shift their gaze within 500ms after appearance of the target to the correct location, defined as an area of 60 pixels radius (depicted as yellow circle) around the target in case of prosaccade trials or around its mirror location in case of antisaccade trials, and to leave it there for at least 100ms.

The task consisted of 3 runs of 4 minutes duration each. Each run comprised 48 active trials, with 4 trials per side (right, left) and condition (antisaccade-reward, antisaccade-punishment, antisaccade-neutral, prosaccade-reward, prosaccade-punishment, and prosaccade-neutral) (see Table 5-2). In addition, each run comprised 4 blank trials, in which no stimuli were displayed. The different types of trials were presented randomly per run.

Table 5-2: Trials per condition, saccade type and side of the screen.

	Condition	Antisaccade		Prosaccade		Total
		Right	Left	Right	Side	
One run	+	4	4	4	4	16
	-	4	4	4	4	16
	o	4	4	4	4	16
	blank					4
	All	12	12	12	12	52
Task (3 runs)	+	12	12	12	12	52
	-	12	12	12	12	52
	O	12	12	12	12	52
	blank					12
	All	36	36	36	36	156

Subjects started with 0.00$ and could win up to 48.00$. Adults won on average 32.8 ± 8.3$, control adolescents won on average 23.7 ± 10.3$, anxious patients won on average 21.9 ± 11.4$, and patients with MDD won on average 25.1 ± 14.0$. An univariate ANOVA revealed a significant difference between groups in terms of money won ($F_{3,86}$ = 5.43, p = 0.002), with post-hoc Scheffé tests

indicating that adults earned significantly more money than healthy adolescents ($p = 0.012$) and adolescents with an anxiety disorder ($p = 0.012$), but not as compared to adolescents with MDD ($p = 0.209$). The three adolescent groups did not differ in terms of money won. Participants were told that they would receive the dollar amount they won, and were sent a check after the completion of the study.

5.2.2 Recording

Eye movements were measured with an ASL Model 504 eye tracking system (Applied Science Laboratories [ASL], Boston, MA). This eye tracking system uses a corneal reflection method with bright pupil technology: The point-of-gaze is determined by relating the corneal reflection of an infrared beam that is projected to the eye, to the center of the illuminated pupil rotating with each eye movement. For this purpose, an auto-focus eye camera and eye illuminator (infrared beam) are contained in a pan-tilt module that automatically moves the camera and illuminator to follow the subjects head. Recordings were taken from the right eye only.

A magnetic head tracker placed behind the subject tracked the position of its head within a specified field by means of a small magnetic sensor that was attached to a baseball hat above the subject's eye (for experimental set-up, see Figure 5-3). Spatial accuracy of this eye tracker is 0.25º visual angle. The range within which valid data can be obtained is 50º visual angle (± 25º) horizontally and 35º visual angle (+ 25º to - 10º) vertically. Sampling rate is 60Hz.

The use of a magnetic head tracker and an auto-focusing lens minimized the possibility of artifacts due to head movements. Nevertheless, participants were instructed to remain still, and a chin rest was employed unless the subject asked not to. Differences in eye-screen distance emerging across subjects were corrected for in the off-line analysis of the raw data. The average distance from the eye to the screen was 66.6 ± 5.2cm (adults: 67.7 ± 5.8cm; control adolescents: 66.5 ± 5.2cm, patients with anxiety disorders: 65.2 ± 3.2cm, patients with MDD: 66.1 ± 5.9cm), with no significant difference between groups ($F_{3,86} = 0.88$, $p = 0.455$).

Following task instructions, subjects were seated in front of the task computer screen and a 9-point eye calibration was performed. Calibration was repeated between task runs as needed. Recordings were obtained in a room lit by standard overhead fluorescent lights.

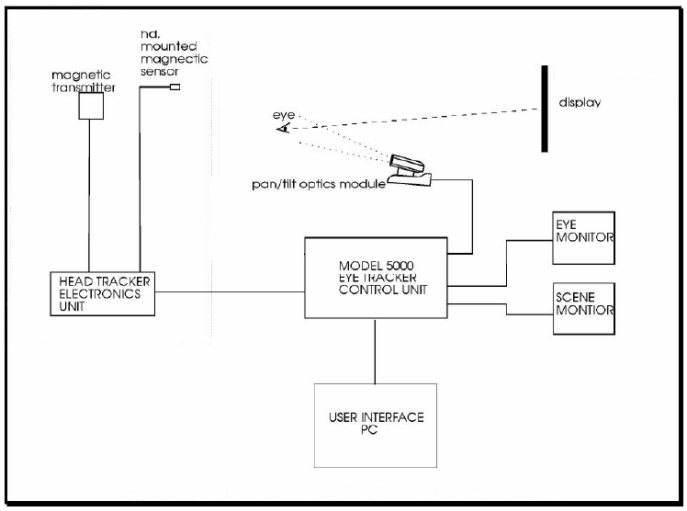

Figure 5-3: Model 504 Eye Tracking system setup with Magnetic Head tracker (adapted from the system setup and operations manual by ASL, version 2.4, 2001).

5.3 Analyses

5.3.1 Data preparation

The raw eye movement data were analyzed off-line. Data on fixations and pupil diameter were extracted from the raw data using software provided by the eye tracking equipment producer ("EYENAL" by Applied Science Laboratories). Data on saccadic eye movements were extracted from the raw data using a MATLAB-based (Mathworks, Natick, MA) program ("ILAB") developed by D. Gitelman from the Northwestern University in Chicago (Gitelman, 2002).

5.3.1.1 Fixation parameters

EYENAL uses an algorithm that identifies a fixation when the point of regard does not change by more than 1° visual angle for 6 or more consecutive data samples. Specifically, fixation onset is defined as the first data sample in a row of 6 or more consecutive data samples during which the point of regard has a standard deviation of below 0.5° visual angle. Fixation offset is defined as the first data sample in a row of 3 consecutive data samples that are further than 1° visual angle from the initial fixation position. With a sampling rate of 60Hz, these criteria lead to minimal fixation duration of 100ms (i.e. 6x16.67ms). Fixation duration after feedback onset was considered for analysis if the fixation had a maximal duration of 1.5sec, which was the case for 93.7% of all fixations analyzed (mean + 2*std = 0.60 + 0.98s). Pupil diameter is given by EYENAL per fixation in pixels and had to be converted to mm based on a scale factor that depends on the magnification of the eye camera lens and distance from the eye to the computer screen of each subject.

5.3.1.2 Saccade parameters

ILAB identifies saccades based on an algorithm developed by Fischer, Gezeck, and Hartnegg (1997; Gitelman, 2002). According to this algorithm, saccade onset is set at the time point at which saccade velocity reaches 30deg/second, and saccade offset at the time point at which it decreases to 15% of its peak. Saccade duration and latency can be evaluated based on the temporal characteristics of the saccadic eye movement, with saccade duration being the time difference between saccade on- and offset, and saccade latency the time difference between target and saccade onset. Saccade direction and amplitude can be evaluated based on the eye position difference between the start and end point coordinates of the saccade (for a graphic illustration of saccade parameter identification by ILAB, see Figure 5-4). Saccade amplitude was measured in degree (°) visual angle, i.e. the distance the eye travels between saccade on- and offset. All data points within an identified saccade with incorrect position information (i.e. coordinates outside the boundaries of the computer screen) or during which the pupillary signal was lost were considered as blink artifacts and the missing data intervals were interpolated.

All first saccades after target onset identified were selected for analysis according to the following criteria: a) the saccadic eye movement had to be directed either to the left or right side of the screen (i.e. to or away from the target), b) had to have an amplitude greater than 1.5° visual angle or smaller than 17° visual angle, and c) had to be initiated within 0 and 700ms after target onset. The lower spatial limit of 1.5° visual angle was set in order to exclude fixational eye movements such as tremor, drifts or fixational microsaccades which rarely are larger than 1° visual angle (e.g. Fischer, 1999, Conde et al., 2004). The upper spatial limit of 17° visual angle was set in order to exclude outliers, with 99% of all first saccades after target onset across all subjects being smaller than 17° visual angle (mean + 2*std = 5.51 + 10.71° visual angle). The time limits were defined a priori based on recommendations by Fischer et al. (1997) assuming that responses above 700ms can not be considered true reactions to a task stimulus (see also Fischer & Weber, 1992; or Klein et al. 2003, 2001, and 2004 using an upper temporal limit of 700ms in their developmental and clinical eye movement studies in children with ADHD). In the current study, 97% of all responses across all subjects had a latency below 700ms (mean + 2*std = 248.02 + 399.92ms). All first saccades that met criteria for analysis were further segregated into three latency categories based on recommendations by Fischer et al. (1997). According to these recommendations, saccades initiated between 0 and 80ms after target onset are considered as anticipatory responses, saccades initiated within 80 and 135 ms as express responses, and saccades with latencies between 135 and 700ms as regular saccades (for review see Fischer, 1999). While anticipatory saccades were not analyzed further in terms of their spatial and temporal characteristics, express and regular saccades were pooled for further analysis since both can be considered true reactions to the target stimuli.

All second saccades after target onset were included in the analysis if they a) occurred after a primary saccade under the antisaccade instruction that fulfilled the above criteria and was directed to the wrong side of the screen, b) had greater amplitudes than the primary incorrect saccade, c) were

directed to the correct side of the screen, and d) had latency below 1850ms. The temporal limit of 1850ms was given by feedback onset occurring 1850ms after target onset (see Figure 5-1).

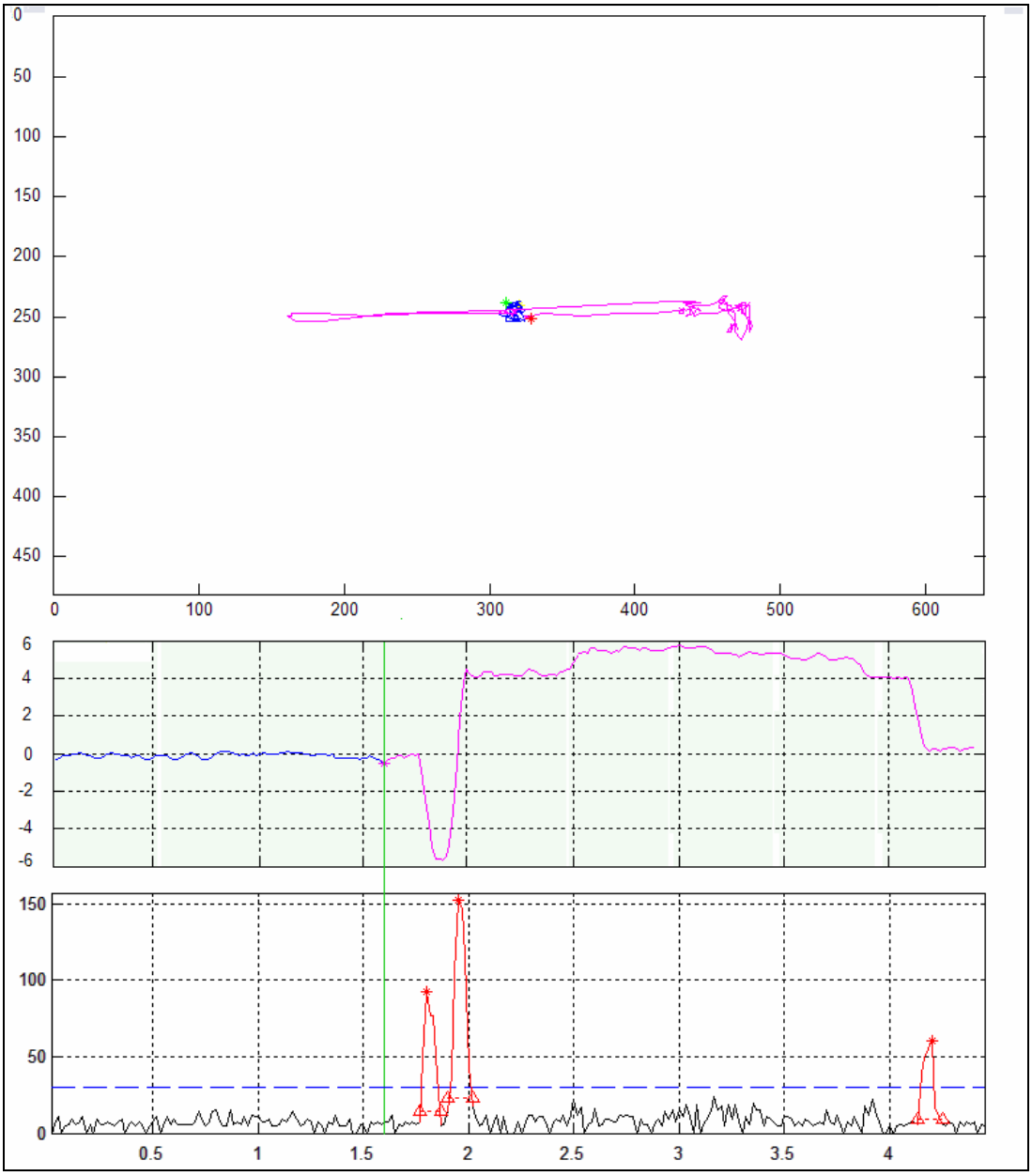

Figure 5-4: Graphic illustration of saccadic eye movement identification and characterization by ILAB (Gitelman, 2002).
Top panel: eye position graph during one trial of the RST task, x-axis horizontal eye position coordinates in pixels, y-axis vertical eye position coordinates in pixels, screen size 600X800 pixels. Blue traces indicate eye position coordinates before target onset, pink traces eye position coordinates after target onset. The green dot indicates the eye position at the start of the trial, the red dot the eye position at the end of the trial. Depicted is an antisaccade trial in which the subject first erroneously looked at the target (left side of the screen) after which he initiated a corrective gaze towards the opposite side of the target (right side of the screen).
Middle panel: Horizontal eye position in degrees visual angle versus time of the RST trial depicted in the top panel, x-axis time in seconds, y-axis degree visual angle. Target onset is indicated by the vertical green line at about 1.6 seconds after cue onset. Blue traces indicate eye position before target onset, pink traces eye position after target onset.
Bottom panel: Velocity plot of the eye movement data shown in the top and middle panel, x-axis time in seconds, y-axis velocity in degrees visual angle per second. Identified saccades are colored in red, their beginnings and endings by triangles, and their peak by an asterix.

5.3.2 Statistics

Two studies were performed, a) a *developmental study* investigating the influence of incentives on cognitive control in adolescents versus adults and b) a *clinical study* investigating the influence of incentives on cognitive control in adolescent mood and anxiety disorders. To this aim, the influence of the three incentive conditions (potential reward, potential punishment, and neutral) on global and dynamic characteristics of saccadic eye movements of differing cognitive demands (antisaccades, prosaccades, and corrective saccades after direction errors) was evaluated. In addition, response to outcome notification was evaluated based on duration of the first fixation after feedback onset and pupil diameter during this fixation as a supplementary index of reward-processing that should be more closely related to consummatory behavior. Data was analyzed using SPSS Version 11.5.1 (SPSS Inc.).

5.3.2.1 Dependant Variables Performance Period

To investigate the effect of incentives on task performance, saccadic responses after target onset were stratified by trial instruction (antisaccade, prosaccade), accuracy (correct, direction errors), and valence (reward, punishment, neutral condition). Saccades were classified as correct if they were directed to the correct side of the screen (to the target in case of prosaccades, to the mirror location of the target in case of antisaccades), and as direction errors if they were directed to the incorrect side of the screen (to the target during antisaccade trial, to the mirror location of the target in case of prosaccade trials). Thus, accuracy criteria differed during actual task performance and during analysis: During task performance, subjects achieved a positive outcome also if they corrected an initial incorrect saccade as long as it happened within 500ms after target onset, while in the analysis the direction of the first saccade determined accuracy. For examples of different accuracy scenarios, see Appendix II, Figure 10-1. Since there was too little data for the analysis of prosaccade direction errors - 10.1% of all recorded direction errors across all subjects occurred during prosaccade trials, and 89.9% during antisaccade trials (see also Appendix II, Figure 10-3) - only correct pro- and antisaccades, and antisaccade direction errors were analyzed. In addition, corrective saccades after an antisaccade direction error were analyzed as an additional index of cognitive control (e.g. initiation of voluntary saccade and error monitoring).

All of the resulting 12 saccade scenarios were characterized by their frequency, latency, peak velocity, amplitude and duration (see Figure 5-5). Frequency was indicated as the proportion of saccadic eye movements of a specific scenario relative to all responses recorded for the given instruction type. For example, percent correct antisaccades during the punishment condition was obtained by dividing the number of all correct antisaccades during the punishment condition of a specific subject by the total number of responses recorded during the antisaccade instruction for this subject, i.e. independent of accuracy and incentive condition. Percent corrected antisaccade direction errors were obtained by dividing the number of corrected antisaccade direction errors in each incentive condition by

the total number of antisaccade direction errors committed during the task. Latency was defined as the time span between target onset and onset of the first saccade in response to it, respectively for corrective saccades as the time span between offset of the first saccade and onset of the corrective saccade.

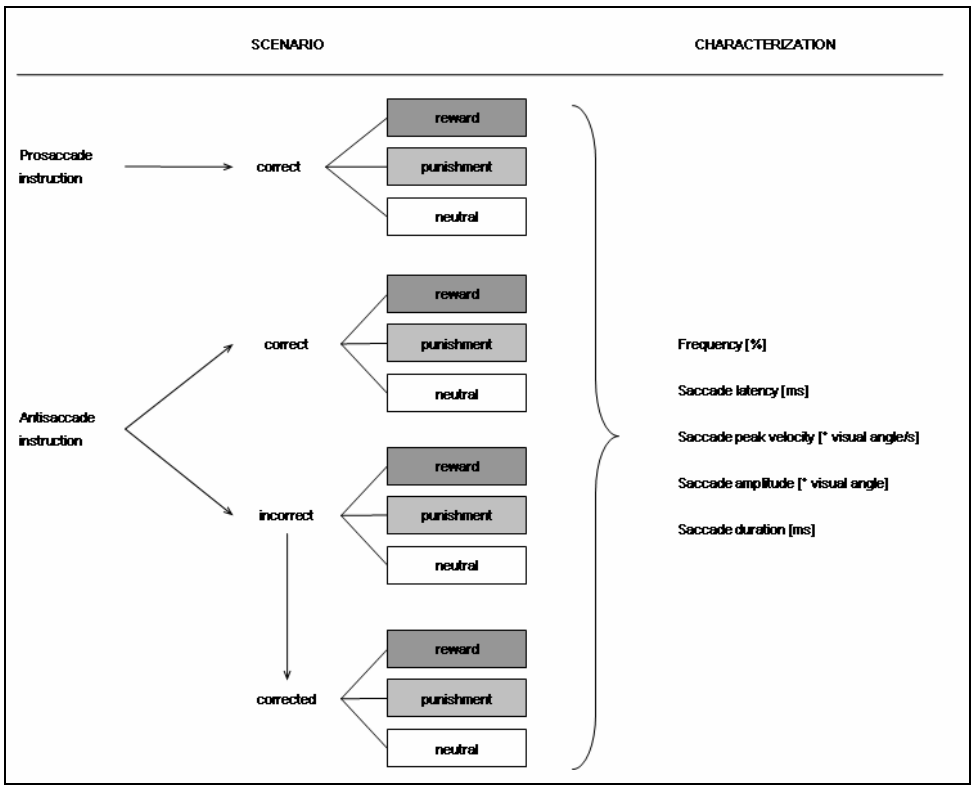

Figure 5-5: All saccadic eye movements of interest (correct prosaccades, correct antisaccades, antisaccade direction errors and corrected antisaccade direction errors) were characterized for each incentive condition (reward, punishment, neutral) separately by their frequency, saccade latency, peak velocity, amplitude and duration.

5.3.2.2 Dependant Variables Outcome notification period

For analysis of response to the different trial outcomes (i.e. winning or not winning 1$, losing or not losing 1$, no monetary consequence), data was stratified per outcome notification (false, true) and valence (reward, punishment, neutral). Of note, outcome was based on performance accuracy criteria as employed during the task (i.e. correct gaze within 500ms after target onset), and not as defined for analysis in the target phase (correct direction of the first saccade after target onset).

Each scenario was characterized by pupil diameter, change in pupil diameter (i.e. pupil dilation) after feedback display, and duration of this fixation (see Figure 5-6). Pupil dilation was obtained by subtracting the mean pupil diameter during the last fixation before feedback onset, from the mean pupil diameter obtained during the first fixation after feedback onset, for each incentive condition, and for each subject. Only those responses were included in the analysis where subjects gazed at the same side of the screen as the feedback was displayed.

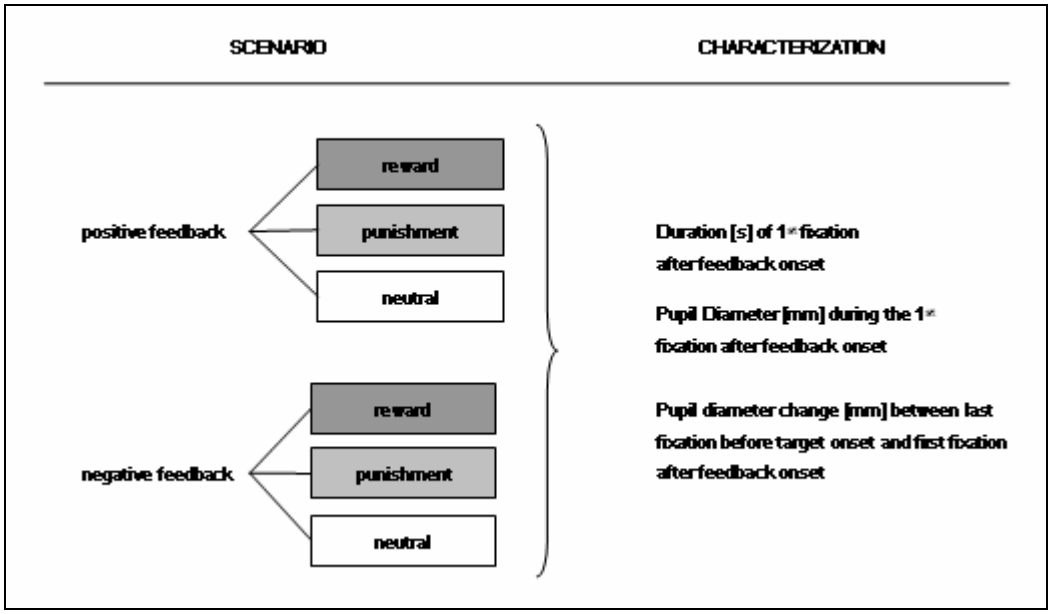

Figure 5-6: All fixations directed at feedback were characterized for each valence condition (reward, punishment, neutral) separately by their duration and the change in pupil diameter.

5.3.2.3 Statistical Procedures

5.3.2.3.1 Analysis of Variance

Eye movement parameters were analyzed with a series of univariate repeated measures Analysis of Variance based on the general linear model method (GLM). *Between subjects factors* were **age** (adults vs. adolescents) for the developmental study and **diagnosis** (healthy adolescents vs. patients with anxiety disorder vs. patients with MDD as primary diagnosis) for the clinical study. *Within subject (repeated measures) factor* for both, developmental and clinical studies was **incentives** (reward condition vs. punishment condition vs. neutral condition). To test if the influence of contingencies differed depending on the level of required cognitive control, an additional within subject factor in the performance period analysis was **type** (correct prosaccades vs. correct antisaccades). Antisaccade direction errors and corrective saccades after direction errors were not included into the within subject factor type because they are related to antisaccade trial performance and/or capture distinct cognitive processes (i.e. error monitoring). For the analysis of the outcome notification period, an additional within subject factor besides incentives was **feedback** (positive vs. negative feedback). For within subject effects and interactions, Roy's largest root multivariate test statistic was employed which has been shown to have superior power relative to other commonly used test statistics such as the Pillai-Bartlett trace test in a concentrated noncentrality data structure, i.e. in a data structure where the means of the dependant variables are expected to capture a common dimension (such as responsiveness to different types of contingencies) (for review see Olson, 1976).

5.3.2.3.2 Post-hoc analyses

Significant main effects of the between subjects factor **diagnosis** were followed up by post-hoc Scheffé tests. For significant main effects of the between subjects factor **age**, no post-hoc tests were necessary since this variable included only two levels.

To explore significant main effects and interactions of the within subject factors **incentives**, **type** and **feedback**, post-hoc independent t-tests (between the two age groups in the developmental study, between any two of the three diagnostic groups in the clinical study) were performed for normally distributed dependent variables, and the Mann-Whitney tests for not normally distributed variables. To test differences between different incentive conditions, types of saccadic responses, or types of feedback, paired sample t-tests for normally distributed dependent variables respectively Wilcoxon tests for not normally distributed variables were performed. Normal distribution of dependent variables per subject group was tested using Kolmogorov-Smirnov tests.

5.3.2.3.3 Significance level

All conclusions of the Analysis of Variance are based on an a priori α of 0.05 unless Levene tests indicated inhomogeneous variances between groups of each study, in which case significance level was lowered to 0.025. However, trends, defined as a significance level below 0.10 (i.e. Luciana et al., 2005) were followed up if considered of relevance for the hypotheses of this study.

T-tests were tested oneway except if otherwise explicitly stated. For multiple post-hoc analysis, the significance level was lowered according to the Bonferroni correction (α' = α / [#of comparisons]).

5.3.2.3.4 Effect size calculation

To measure the strength of the relationship between independent and dependent variables, effect sizes were determined for any significant effect or trend reported. For Analysis of Variance, $\acute{\eta}_p^2$ was indicated, which is calculated by SPSS and defined as the ratio of the effect variance to the effect and its error variance, i.e. $\acute{\eta}_p^2 = s^2_{effect} / (s^2_{effect} + s^2_{error\ for\ effect})$ (Cohen, 1988). According to Cohen (1988), a $\acute{\eta}^2$ of 0.01 can be considered a small effect, a $\acute{\eta}^2$ of 0.06 can be considered a medium effect, and $\acute{\eta}^2$ of 0.14 a large effect. According to Barnette (2006), $\acute{\eta}_p^2$ is interpreted in the same way as $\acute{\eta}^2$.

For post-hoc independent sample t-tests, Cohen's d was calculated as the mean of the dependant variable in the first subject group minus the mean of the dependant variable in the second subject group, divided by the pooled standard deviation of both samples (i.e. the square root of the average of the two squared standard deviations), i.e. $d = \bar{x}_1 - \bar{x}_2 / \sqrt{[(\sigma_1^2 + \sigma_2^{2)}/2]}$ (Rosnow & Rosenthal, 1996). For paired-sample t-tests, Cohen's d_z was calculated as the mean of the first measurement in

one sample minus the mean of the second measurement in this sample, divided by the standard deviation of the difference of those means, i.e. $d_z = \bar{x}_d / \sigma_d$ (Cohen, 1988). Cohen indicates a d of ± 0.2 as a small effect, a d of ± 0.5 as a medium effect, and a d of ± 0.8 as a large effect. However, although widely in use, these criteria levels given for evaluation of the strength of an effect were not intended by Cohen to be used in practice and need to be treated with caution (Barnette, 2006).

For Mann-Whitney independent-sample tests, θ was calculated as an indicator of effect size, which is defined by Newcombe (2006) as the Mann-Whintey-U value divided by the product of both sample sizes, i.e. $\theta = U/(n1*n2)$. According to an analysis by Newcombe (2006), a θ of 0.50 corresponds to Cohen's d of 0.00, and θ of 0.45 respectively of 0.55 to a Cohen's d of ± 0.18, and thus may be considered weak. Finally, for Wilcoxon paired-sample t-test and Kruskal-Wallis-test for independent samples, no widely used indicator of effect size could be found in the statistical literature and thus effect size is not reported for these non-parametric statistical tests.

6. Results

6.1 General characteristics of data analyzed

Overall, there was little loss of data due to subjects missing a trial or the eye camera losing the pupillary signal. Specifically, on 97.87 ± 2.41% of all 144 active trials of the RST task a saccadic eye movement was identified after target onset that had an amplitude between 1.5 and 17° visual angle and went either to the left or to right side of the screen. The four subject groups did not differ in the amount of saccadic responses recorded ($F_{3,86}$ = 1.36, p = 0.261, for proportion of saccades recorded per subject group, see Table 9-1).

Of all saccadic responses after target onset identified that went either to the right or left side of the task screen, 1.61 ± 1.93% were anticipatory (i.e. had latencies below 80ms), 10.54 ± 12.56% had latencies in the range of express saccades (between 80 and 134ms), 86.97 ± 13.11 in the range of regular saccades (between 135 and 700ms), and 0.89 ± 1.41% were classified as late (latency above 700ms). The four subject groups did not differ in terms of the proportion of saccadic responses per latency category recorded (anticipatory saccades: $F_{3,86}$ = 1.05, p = 0.374; express saccades: $F_{3,86}$ = 0.79, p = 0.503; regular saccades: $F_{3,86}$ = 1.04, p = 0.381; late saccades: $F_{3,86}$ = 1.28, p = 0.288; for proportion of saccades recorded per subject group and latency category, see Table 9-1).

Of all true saccadic responses, i.e. those with latencies between 80 and 700ms after target onset that went either to the left or right side of the task screen, 49.67 ± 2.60% across all subjects were recorded during antisaccade trials and 50.33 ± 2.60% during prosaccade trials. Of those true saccadic responses recorded during antisaccade trials, 67.60 ± 19.10% across all subjects were correct and the remaining 32.40 ± 19.10% were direction errors, of which 78.12 ± 20.36% were corrected according to the criteria specified in chapter 5.3.2.1. Finally, 96.53 ± 4.41% of all true saccadic responses recorded during the prosaccade instruction were correct, with large variations in the proportion of prosaccade direction errors being corrected across all subjects (49.86 ± 40.12%). For proportion of correct and incorrect saccades per subject group and saccade type, see Table 9-1; for saccadic reaction time distributions per subject group and accuracy, see Figure 10-2 and Figure 10-3.

During outcome notification, 90.63 ± 8.08% of all possible responses (i.e. fixations after feedback onset in 144 active trials per task) were recorded by the eye tracker. Loss of data was due to similar reasons as during the performance period of the task, i.e. subjects missing feedback, blinking, or the eye camera losing the pupillary signal. Of all fixations recorded, 93.43 ± 6.45% were directed at the side of the screen where the feedback was displayed and thus included into the analysis, with no difference between the four groups ($F_{3,86}$ = 1.03, p = 0.382). Finally, of those responses directed at the feedback display, 23.40 ± 11.89 received negative feedback (i.e. monetary loss, no win, or notification of incorrect performance on neutral trials), and 76.60 ± 11.89 positive feedback (monetary win, no loss or notification of correct performance on neutral trials). For proportion of fixations recorded after feedback display, and directed at positive and negative feedback per subject group, see Table 9-2.

6.2 Developmental Study

6.2.1 Self-Report Measures

The two groups did not differ significantly in their emotional state at the time of testing as evident by a lack of significant group differences in the state version of the Spielberger State-Trait Anxiety Inventory (T_{47} = -0.82, p = 0.207). However, there was a significant difference between age groups on the trait form of the Spielberger State-Trait Anxiety Inventory (T_{48} = -1.89, p = 0.032, d = 0.53) indicating that adolescents generally felt more anxious than adults (see also Figure 10-4). Results of the Depression Inventories were not compared between age groups since different forms were used for adults (Beck Depression Inventory) and Adolescents (Children Depression Inventory).

In addition, there were differences between age groups in the Debriefing Questionnaire performed after completion of the eye tracking task (see Figure 10-5). Specifically, adolescents reported to have been more bored by the task than adults (Z = -2.71, p = 0.007, θ = 0.29), to have become more tired during the task than adults (Z = -1.78, p = 0.075, θ = 0.36), to have had more difficulty staying focused (Z = -2.62, p = 0.009, θ = 0.30), and finally to have had more difficulty sitting still (Z = -2.36, p = 0.018, θ = 0.32). In addition, adolescents thought more often than adults that the task was rigged (manipulated) by the experimenters (Z = -2.35, p = 0.019, θ = 0.37) and they reported more often than adults to have tried to guess on which side of the screen the target would appear (Z = -2.44, p = 0.015, θ = 0.32). Both groups rated money as similarly incentive (Z = -1.03, p = 0.303; θ = 0.38). Importantly, they did not differ in their reported ability to distinguish the colors grey and white (Z = -0.09, p = 0.931, θ = 0.49). For a listing of group differences on all items of the debriefing questionnaire, see Table 9-9.

6.2.2 Homogeneity of Variance and Distribution of data

Kolmogorov-Smirnov goodness-of-fit tests conducted per age groups indicated normal distribution for the majority of dependant variables of the performance period analyzed in both groups except for some of the characteristics of antisaccade direction errors and their corrections (see Table 9-5). For the dependant variables of the outcome notification period, Kolmogorov-Smirnov goodness-of-fit tests indicated throughout normal distribution (Table 9-6). For those variables for which no normal distribution of data can be assumed, non-parametric post-hoc tests were applied to follow up significant interactions of the Analysis of Variance.

Levene tests for homogeneity of variance indicated inhomogeneous variances for several global and dynamic characteristics of saccadic eye movements, in particular of correct prosaccades (see Table 9-7). For the feedback period, all variables analyzed had homogenous variances (Table 9-8). The significance level for variables with inhomogeneous variances was lowered in the Analysis of Variance to 0.025.

6.2.3 Significant main effects and interactions performance period

Significant main effects and interactions of the Analysis of Variance will be outlined per between and within subject's factors in the subsequent sections. For an overview of all effects and interactions, see Table 9-10.

6.2.3.1 Age-related differences in task performance

Groups differed in their global task performance as indicated by a main effect of **age** for *percent correct responses* ($F_{1,60}$ = 11.32, p ≤ 0.025, $ή_p^2$ = 0.16). This main effect was modulated by **type** of saccadic eye movement ($F_{1,60}$ = 8.68, p ≤ 0.025, $ή_p^2$ = 0.13). Analysis of Variance per saccade type and examination of descriptives and graphs (see Figure 10-6) indicated that groups did not differ in terms of *percent correct prosaccades* ($F_{1,60}$ = 3.02, p = 0.087), but in *percent correct antisaccades* ($F_{1,60}$ = 10.85, p ≤ 0.025, $ή_p^2$ = 0.15), with adults making significantly more correct antisaccades per incentive condition (adults: 25.90 ± 5.29%; adolescents: 21.27 ± 7.11%) and committing less antisaccade direction errors per incentive condition than adolescents (adults: 7.44 ± 5.23%; adolescents: 12.07 ± 7.01%).

In addition, **age groups** differed in dynamic indicators of task performance such as *latency* and *peak velocity of correct responses*, both of which depended on saccade **type** (saccade latency: $F_{1,60}$ = 8.60, p ≤ 0.025, $ή_p^2$ = 0.10; saccade peak velocity: $F_{1,60}$ = 6.33, p ≤ 0.025, $ή_p^2$ = 0.10): While both groups had comparable *prosaccade latency* ($F_{1,60}$ = 1.46, p = 0.232) and *prosaccade peak velocity* ($F_{1,60}$ = 0.003, p = 0.957), they differed in these measures for correct antisaccades (latency: $F_{1,60}$ = 11.49, p ≤ 0.05, $ή_p^2$ = 0.16; peak velocity: $F_{1,60}$ = 4.06, p ≤ 0.05, $ή_p^2$ = 0.06), with adults *initiating correct antisaccades* across incentive conditions earlier than adolescents (adults: 260.85 ± 28.83ms; adolescents: 290.86 ± 47.03ms), and adolescents having faster *antisaccade peak velocities* than adults (adults: 95.21 ± 18.14° visual angle/s; adolescents: 105.08 ± 26.32° visual angle/s, see also Figure 10-6). Finally, there was a highly significant effect of **age** for *latency of corrective saccades* ($F_{1,48}$ = 22.05, p ≤ 0.025, $ή_p^2$ = 0.32) with adults having overall shorter correction times than adolescents (adults: 124.87 ± 79.90ms; adolescents: 229.63 ± 139.23 ms).

6.2.3.2 Incentive-related modulation of task performance

6.2.3.2.1 Effect of Incentives on global performance measures

The incentive manipulation clearly influenced global task performance on all primary saccades as indicated by a significant main effect of **incentives** for *percent correct responses* ($F_{2,59}$ = 18.99, p ≤ 0.025, $ή_p^2$ = 0.24) which differed between saccade **type** ($F_{2,59}$ = 18.43, p ≤ 0.025, $ή_p^2$ = 0.23), and a significant main effect of **incentives** for *percent antisaccade direction errors* ($F_{2,59}$ = 14.17, p ≤ 0.025, $ή_p^2$ = 0.32). However, there were no significant interactions of **incentives** with **age**, indicating that the

two groups modulated frequency variables similarly by incentives. Results of all paired-sample post-hoc tests mentioned subsequently are summarized in Table 9-11 and descriptives in Table 9-3.

Post-hoc paired-sample t-tests and examination of descriptives and graphs (see Figure 10-6) indicated that subjects made most *correct prosaccades* on the reward (33.29 ± 2.05%) and the fewest on the punishment condition (31.24 ± 3.09%; reward – punishment: $T_{61} = 4.03$, $p < 0.017$, $d = 0.51$; reward – neutral: $T_{61} = 3.62$, $p < 0.017$, $d = 0.46$; punishment – neutral: $T_{61} = -1.46$, $0.05 \leq p \leq 0.10$, $d = -0.19$). For *antisaccades*, subjects made significantly more correct responses on both incentive conditions (reward: 24.46 ± 5.71%, punishment: 25.17 ± 7.09%) as compared to the neutral condition (20.89 ± 7.29%; reward – neutral: $T_{61} = 4.85$, $p < 0.017$, $d = 0.62$; punishment – neutral: $T_{61} = 5.88$, $p < 0.017$, $d_z = 0.75$), and committed less direction errors on the reward (8.79 ± 5.91%) and punishment conditions (8.51 ± 6.80%) as compared to the neutral condition (12.18 ± 7.12%; reward – neutral: $T_{61} = -4.71$, $p < 0.017$, $d_z = -0.60$; punishment – neutral: $T_{61} = -5.33$, $p < 0.017$, $d_z = -0.68$).

6.2.3.2.2 Effect of Incentives on dynamic performance measures

Incentives also influenced the dynamic characteristics of task performance such as reaction time measures, saccade peak velocity and saccade amplitude, but not saccade duration. Although descriptives and graphs pointed out several differences in groups in modulation of these measures, few of them reached significance level in the Analysis of Variance. However, since differences between groups in incentive-related modulation of task performance were the main focus of the current study, post-hoc tests were not only applied to significant main effects and interactions of the Analysis of Variance, but in an exploratory manner to all variables where group differences could be expected based on results from non-human primate studies and involvement of brain circuits known to undergo developmental alterations during adolescence. This were namely reaction time measures which reportedly are based on prefrontal neural circuits (for review see Munoz & Everling, 2004) (see chapter 3.2.1.2), and peak velocity which concerns aspects of motor regulation that depend on basal ganglia/prefrontal pathways (Kawagoe et al., 1998)

Reaction Time Measures

For reaction time measures, there was a trend for a modulation by **incentives** for *latency of correct saccades* ($F_{2,59} = 2.71$, $0.05 \leq p \leq 0.10$, $\acute{\eta}_p^2 = 0.08$), and a significant main effect of **incentives** for *latency of corrective saccades* which differed between **age** groups ($F_{2,47} = 4.85$, $p \leq 0.05$, $\acute{\eta}_p^2 = 0.16$).

Post-hoc analysis indicated that subjects across age groups *initiated correct saccades* later on the punishment (223.98 ± 29.27ms) as compared to the reward (218.45 ± 24.39ms) and neutral conditions (219.22 ± 30.55ms, punishment - reward: $T_{61} = -2.68$, $p < 0.017$, $d = -0.34$; punishment – neutral: $T_{62} = 2.46$, $p < 0.017$, $d = 0.31$). Exploratory paired-sample t-tests performed per age group indicated

that this modulation across subjects was mainly brought about by adolescents on prosaccade trials (see also Figure 10-6). Specifically, while adults did not show a significant incentive-related modulation of latency of correct pro- or antisaccades, adolescents initiated correct prosaccades significantly later on the punishment (192.06 ± 30.91ms) relative to the reward condition (186.16 ± 26.71ms, punishment – reward: $T_{31} = -2.42$, $p < 0.017$, $d_z = -0.43$). This prolongation of prosaccade initiation resulted on independent-sample t-tests in a trend for a group difference between adolescents and adults for the punishment condition ($T_{60} = -1.58$, $p \leq 0.10$, $d = -0.40$). Of note, effect sizes obtained for this exploratory post-hoc analysis indicated that albeit not reaching significance level in the Analysis of Variance, the effects observed can be considered practically relevant (d or $d_z > 0.4$, see also discussion in chapter 7.3).

A similar pattern of modulation could be observed for *latency of antisaccade direction errors* during the reward condition: while adults did not show significant differences between any two of the three incentive conditions for this measure in exploratory post-hoc paired-sample t-tests, adolescents had increased latencies on the reward condition (206.79 ± 59.22ms) as compared to the neutral condition (183.73 ± 36.58ms; $T_{31} = 2.43$, $p < 0.017$, $d_z = 0.43$) and on a trend level on the punishment condition (186.60 ± 37.43ms; $T_{31} = 1.98$, $0.017 \leq p \leq 0.05$, $d_z = 0.36$). This prolongation of initiation of a direction error on the reward condition for adolescents lead to a significant difference for this measure as compared to adults (reward condition: 182.74 ± 42.70ms; $T_{55} = -1.71$, $p \leq 0.05$, $d = -0.47$).

In terms of *latency of corrective saccades*, where there was a significant age-by-incentives interaction, paired-sample t-tests performed for each group separately and examination of descriptives and graphs (see Figure 10-6) indicated that adolescents initiated corrective saccades significantly earlier for the reward (198.65 ± 112.27ms) as compared to the neutral condition (280.85 ± 154.47ms; $T_{28} = -3.12$, $p < 0.017$, $d_z = -0.58$), and on a trend level earlier on the punishment condition (209.39 ± 150.95ms) as compared to the neutral condition ($T_{28} = -1.76$, $0.017 \leq p \leq 0.05$, $d_z = -0.33$). Adults in contrast showed a trend for *slower* initiation of corrective saccades on the reward condition (154.10 ± 107.35ms) as compared to the neutral condition (108.75 ± 64.92ms; reward – neutral: $T_{23} = 1.71$, $0.017 \leq p \leq 0.05$, $d_z = 0.35$), but not as compared to the punishment condition (111.77 ± 67.13ms). Independent-sample t-tests revealed significant differences between age groups for the punishment ($T_{54} = -2.84$, $p \leq 0.05$, $d = -0.84$) and neutral condition ($T_{43.54} = -5.15$, $p \leq 0.05$, $d = -1.45$).

Saccade Peak Velocity

For saccade peak velocity, there was a small trend for an **incentive**-related modulation of *peak velocity of correct saccades* that however reached medium-level effect size ($F_{2,59} = 2.38$, $0.05 \leq p \leq 0.11$, $\acute{\eta}_p^2 = 0.08$), and a significant **incentive**-related modulation of *peak velocity of antisaccade direction errors* ($F_{2,52} = 3.44$, $p \leq 0.05$, $\acute{\eta}_p^2 = 0.12$) and *peak velocity of corrective saccades* ($F_{2,47} = 4.34$, $p \leq 0.025$, $\acute{\eta}_p^2 = 0.16$).

Post-hoc within-group tests and examination of descriptives and graphs (see Figure 10-6) indicated that for all saccade types, peak velocities were higher on the reward as compared to the neutral condition (*peak velocity of correct responses*, reward condition: 96.08 ± 12.98° visual angle/s; neutral condition: 92.66 ± 13.81° visual angle/s; $T_{61} = 2.91$, $p < 0.017$, $d_z = 0.37$; *peak velocity of antisaccade direction errors*, reward condition: 98.70 ± 48.25° visual angle/s; neutral condition: 83.63 ± 21.71° visual angle/s; $Z = -2.48$, $p < 0.017$; *peak velocity of corrective saccades*, reward condition: 170.14 ± 44.93° visual angle/s; neutral condition 152.38 ± 30.94° visual angle/s; $Z = -2.91$, $p < 0.017$).

Incentive modulation did not differ significantly between age groups for any saccade type in the Analysis of Variance. However, exploratory post-hoc paired-sample t-tests indicated a pattern that was very reminiscent of that obtained for reaction times measures. Specifically, while within-group post-hoc tests revealed no significant modulation by incentives for peak velocity for any primary saccades in the adult subject group, adolescents had significantly faster *peak velocity of prosaccades* during the punishment condition (92.94 ± 13.26° visual angle/s) as compared to the neutral condition (88.62 ± 11.03° visual angle/s; $T_{31} = 2.65$, $p < 0.017$, $d_z = 0.47$) and faster *peak velocity of antisaccade direction errors* on the reward condition (104.37 ± 48.60° visual angle/s) as compared to the neutral condition (82.49 ± 10.46° visual angle/s; $Z = 2.15$, $p < 0.017$). The speeding of peak velocity on these two measures by adolescents led to trend for a between-group difference for peak velocity of antisaccade direction errors on the reward condition (adults: 91.45 ± 47.78° visual angle/s; $Z = -1.51$, $0.05 \leq p \leq 0.10$, $\theta = 0.38$).

Saccade Amplitude

For *amplitude* of *corrective saccades* there was a significant main effect of **incentives** ($F_{2,47} = 4.55$, $p \leq 0.05$, $\acute{\eta}_p^2 = 0.16$) that differed between **age groups** ($F_{2,47} = 3.40$, $p \leq 0.05$, $\acute{\eta}_p^2 = 0.13$). Wilcoxon tests performed for each group separately indicated that while adolescents did not modulate amplitudes of corrective saccades by incentive condition (reward condition: 9.52 ± 2.04° visual angle; punishment condition: 9.26 ± 1.46° visual angle; neutral condition: 9.30 ± 1.65° visual angle), adults had significantly smaller amplitudes of corrective saccades on the punishment (9.38 ± 1.75° visual angle) as compared to the reward condition (10.86 ± 2.18° visual angle; $Z = -3.19$, $p < 0.017$), and the neutral condition (10.66 ± 7.92° visual angle; $Z = -2.71$, $p < 0.017$). However, there were no significant group differences for any single incentive condition of this measure as indicated by Mann-Whitney-U tests.

6.2.3.3 Saccade type related differences in task performance

Correct prosaccades and correct antisaccades differed on all characteristics investigated. Although differences between these two types of saccadic eye movements were not the main focus of this study, they may serve as an important validation for the data obtained, since differences between

pro- and antisaccade performance are well documented in the eye movement literature (see chapter 3.1). In line with previous research, there were more correct pro- than antisaccades across age groups (32.14 ± 2.59% vs. 23.51 ± 6.69%), indicating the higher cognitive demand of performing a correct antisaccade irrespective of age ($F_{1,60}$ = 166.39, p ≤ 0.025, $ή_p^2$ = 0.74). In addition, correct antisaccades were initiated later than correct prosaccades (276.34 ± 41.86ms vs. 184.95 ± 27.54ms; $F_{1,60}$ = 450.61, p ≤ 0.025, $ή_p^2$ = 0.88), also in line with previous research and supporting the notion that antisaccade performance requires more computational processes than prosaccade performance. Finally, antisaccades had faster peak velocities than prosaccades (100.30 ± 23.20° visual angle/s vs. 90.97 ± 11.74° visual angle/s; $F_{1,60}$ = 21.24, p ≤ 0.025, $ή_p^2$ = 0.26), longer saccade durations (119.48 ± 18.42ms vs. 105.58 ± 9.05ms; $F_{1,60}$ = 61.23, p ≤ 0.05, $ή_p^2$ = 0.50), and larger saccade amplitudes (5.90 ± 1.42° visual angle vs. 4.91 ± 0.41±; $F_{1,60}$ = 45.50, p ≤ 0.025, $ή_p^2$ = 0.43). While faster antisaccade peak velocities were mainly observed in adolescents, saccade duration and amplitude did not differ between groups (see chapter 6.2.3.1). In particular higher peak velocities and larger saccade amplitudes of antisaccades as compared to prosaccades contradict findings from the eye movement research conducted in humans under non-incentive conditions, however, a large influence of incentives for peak velocities of internally-guided saccades and their spatial accuracy has commonly been observed in non-human primates (Kawagoe et al., 2002; Kobayashi et al., 2002; Leon & Shadlen,1999; Takikawa et al., 2002; Roesch & Olson, 2003), suggesting that in the current study, the incentive nature of the RST might have had a stronger influence on peak velocity and amplitude of antisaccades as compared to visually-guided prosaccades.

6.2.4 Significant main effects and interactions outcome notification period

Significant main effects and interactions of the Analysis of Variance will be outlined per dependant variable in the subsequent sections. For an overview of significant main effects and interactions, see Table 9-12, results of dependant-sample post-hoc tests mentioned below are summarized in Table 9-13 and descriptives in Table 9-4.

6.2.4.1 Fixation Duration

Duration of the first fixation after feedback onset was modulated differently by **feedback** type ($F_{1,57}$ = 19.20, p ≤ 0.05, $ή_p^2$ = 0.25), with positive feedback leading to longer fixation durations across subjects (0.53 ± 0.07s) than negative feedback (0.48 ± 0.12s, see also see Figure 10-7). However, there was no significant modulation of fixation duration by **incentives** or **age**, or interactions thereof.

6.2.4.2 Pupil diameter

There were several main effects for *pupil diameter during the first fixation after feedback onset*. First, pupil diameter differed between **age** groups ($F_{1,57}$ = 24.57, $p \leq 0.05$, $\acute{\eta}_p^2$ = 0.30), with adolescents having larger pupil diameters than adults (adolescents: 7.32 ± 1.53mm; adults 5.62 ± 1.20mm, see also Figure 10-7). In addition, pupil diameter differed between **feedback** type ($F_{1,57}$ = 79.80, $p \leq 0.05$, $\acute{\eta}_p^2$ = 0.58), with pupil diameter across groups being larger for negative (6.57 ± 1.59mm) than positive feedback (6.42 ± 1.63mm). Finally, there was a main effect of **incentives** for pupil diameter ($F_{2,56}$ = 23.41, $p \leq 0.05$, $\acute{\eta}_p^2$ = 0.46), with post-hoc paired-sample t-tests indicating that subjects had larger pupil diameter for both incentive conditions (reward condition: 6.48 ± 1.61mm; punishment condition: 6.47 ± 1.62mm) as compared to the neutral condition (6.40 ± 1.64mm; reward – neutral: T_{61} = 5.29, $p < 0.017$, d_z = 0.67; punishment – neutral: T_{31} = 5.21, $p < 0.017$, d_z = 0.66). This effect of **incentives** in addition differed between **feedback** type ($F_{1,56}$ = 4.22, $0.017 \leq p \leq 0.05$, $\acute{\eta}_p^2$ = 0.13). Paired-sample t-tests per feedback type indicated that pupil diameter was modulated similarly by incentives for both types of feedback, with pupil diameter being larger for both incentive conditions as compared to the neutral condition (*negative feedback*: reward condition: 6.62 ± 1.58mm, punishment condition: 6.65 ± 1.61mm; neutral condition: 6.50 ± 1.62mm; reward – neutral: T_{59} = 5.35, $p < 0.017$, d_z = 0.69, punishment - neutral: T_{59} = 4.47, $p < 0.017$, d_z = 0.58; *positive feedback*: reward condition: 6.45 ± 1.62mm; punishment condition: 6.43 ± 1.63mm; neutral condition: 6.37 ± 1.65mm; reward – neutral: T_{61} = 4.59, $p < 0.017$, d_z = 0.58; punishment – neutral: T_{61} = 3.95, $p < 0.017$, d_z = 0.50). However for positive but not negative feedback there was in addition a trend for pupil diameter being larger on reward as compared to punishment trials (T_{61} = 1.41, $0.05 \leq p \leq 0.10$, d_z = 0.18).

The main effects for pupil diameter during the first fixation after feedback onset differed for some variables between age groups. Specifically, there was a significant **age-by-incentives** interaction ($F_{2,56}$ = 3.43, $p \leq 0.05$, $\acute{\eta}_p^2$ = 0.11), and a trend for an **age-by-feedback** interaction ($F_{1,57}$ = 3.65, $0.05 \leq p \leq 0.10$, $\acute{\eta}_p^2$ = 0.06) which was followed up being of interest for the hypothesis of this thesis and having sufficiently large, i.e. medium effect sizes ($\acute{\eta}_p^2 < 0.06$, see also chapter 5.3.2.3.4).

Post-hoc paired-sample t-tests conducted per age group across feedback type indicated that the larger pupil diameter observed for contingent conditions as compared to the neutral condition was true for both age groups, but was in terms of effect size and significance level more pronounced in adults as compared to adolescents (*adults*: reward: 5.59 ± 1.16mm; punishment: 5.58 ± 1.18mm; neutral: 5.49 ± 1.23mm; reward – neutral: T_{29} = 4.17, $p < 0.017$, d_z = 0.76; punishment – neutral: T_{29} = 5.17, $p < 0.017$, d_z = 0.94; *adolescents*: reward: 7.31 ± 1.53mm; punishment: 7.30 ± 1.54mm; neutral: 7.24 ± 1.53mm; reward – neutral: T_{31} = 3.29, $p < 0.017$, d_z = 0.58; punishment – neutral: T_{31} = 2.63, $p < 0.017$, d_z = 0.47). Independent-sample t-tests indicated that the two age groups differed on all three incentive conditions, with no difference being stronger relative to the others (reward: T_{60} = -4.90, $p < 0.017$, d = -1.25, punishment: T_{60} = -4.95, $p < 0.017$, d = -1.26; neutral: T_{60} = -4.94, $p < 0.017$, d = -1.26). Post-hoc paired-sample t-tests per subject group and feedback type indicated that adults as compared to adolescents had more pronounced difference in pupil diameter between negative (5.53 ±

1.20mm; adolescents: 7.25 ± 1.55 mm) and positive feedback (5.70 ± 1.19mm; adolescents: 7.37 ± 1.51mm; $T_{29} = 6.34$, $p \leq 0.025$, $d_z = 1.16$), however, the difference between pupil diameter for positive and negative feedback reached high significance for adolescents as well ($T_{31} = 5.30$, $p \leq 0.025$, $d_z = 0.94$).

6.2.4.3 Pupil dilation

The results on *pupil dilation* after feedback onset corroborated those reported for absolute pupil diameter after feedback onset reported above, although reaching smaller significance levels and effect sizes. Specifically, pupil dilation differed on a trend level between **age** groups ($F_{1,57} = 3.61$, $p = 0.05 \leq p \leq 0.10$, $\acute{\eta}_p^2 = 0.06$) with adults having greater change of pupil diameter after feedback onset as compared to adolescents (adults: 0.014 ± 0.083mm; adolescents: 0.008 ± 0.059mm; see also Figure 10-7); it differed significantly between **feedback** type ($F_{1,57} = 20.74$, $p \leq 0.05$, $\acute{\eta}_p^2 = 0.27$) with larger pupil dilation for negative (0.048 ± 0.093mm) than positive feedback (0.003 ± 0.078mm); and finally pupil dilation differed on a trend level between **incentives** ($F_{2,56} = 3.06$, $0.05 \leq p \leq 0.10$, $\acute{\eta}_p^2 = 0.10$) which similarly to pupil diameter additionally depended on feedback type ($F_{2,56} = 4.96$, $p \leq 0.05$, $\acute{\eta}_p^2 = 0.15$).

Post-hoc paired-sample t-tests across groups per feedback type indicated that for *negative feedback*, subjects dilated pupil diameter stronger for the reward (0.063 ± 0.119mm) as compared to the neutral condition (0.029 ± 0.073mm; reward – neutral: $T_{59} = 2.99$, $p < 0.017$, $d_z = 0.39$), while for *positive feedback* pupil diameter contracted for the punishment condition (-0.006 ± 0.078mm) and dilated for the neutral condition (0.012 ± 0.069mm, punishment – neutral: $T_{61} = -2.31$, $p < 0.017$, $d_z = -0.29$).

Since it was hypothesized that adults would be more affected by negative feedback than adolescents, exploratory paired-sample t-tests within each age group were conducted. Results confirmed this hypothesis, showing that the above reported enhanced dilation after receiving notification of negative outcome for reward trials was largely based on the adult sample (reward condition: 0.096 ± 0.090mm; neutral condition: 0.037 ± 0.081mm; reward – neutral: $T_{27} = 3.19$, $p < 0.017$, $d_z = 0.60$), who additionally showed a trend for greater pupil dilation for the punishment (0.078 ± 0.15mm) as compared to the neutral condition ($T_{26} = 1.84$, $p < 0.05$, $d_z = 0.35$). In contrast, adolescents did not show a significant within-group modulation by incentive condition of pupil dilation for negative feedback. In contrast, significant constriction of pupil diameter after receiving positive feedback for the punishment condition as compared to the neutral condition could only be observed on a trend level in adolescents (punishment: -0.014 ± 0.081mm; neutral condition: 0.012 ± 0.053mm; $T_{31} = -2.07$, $0.017 \leq p \leq 0.05$, $d_z = -0.37$) but not in adults. Finally, independent sample t-tests indicated that the observed pupil dilation in adults, but not adolescents after receiving negative feedback for incentive conditions, lead to a significant difference between these two groups for the reward condition ($T_{58} = 2.88$, $p \leq 0.05$, $d = 0.82$), and on a trend level for the punishment condition ($T_{58} = 1.50$, $0.05 \leq p \leq 0.10$, $d = 0.42$).

6.3 Clinical Study

6.3.1 Self-Report Measures

The three diagnostic groups differed in their emotional state at the time of testing as revealed by Oneway Analysis of Variance with significant main effects or trends of **diagnosis** for the Spielberger State-Trait Anxiety Inventory state ($F_{2,36}$ = 3.02, p = 0.061) and trait version ($F_{2,36}$ = 22.08, p = 0.000), and for the Children Depression Inventory (CDI) ($F_{2,47}$ = 12.56, p = 0.000). Post-hoc Scheffé tests indicated that both patient groups were significantly more anxious than controls (STAI trait: controls vs. anxious patients p = 0.000; controls vs. depressed patients p = 0.000) and scored significantly higher on the Child Depression Inventory than controls (CDI: controls vs. anxious patients p = 0.006; controls vs. depressed patients p = 0.000), however, the self-report measures did not differentiate between the two patient groups (STAI trait: anxious vs. depressed patients p = 0.193; CDI anxious vs. depressed patients p = 0.150, see also Figure 10-8).

In terms of the debriefing questionnaire filled out after completion of the RST, a Kruskal-Wallis test - employed due to the ordinal scaling of the ratings - revealed no significant group differences (Table 9-14). However, there were trends for groups to differ in their ratings on three questions, namely boredom during the task ($\chi^2_{df=2}$ = 5.20, p = 0.074), upset when receiving negative feedback ($\chi^2_{df=2}$ = 4.79, p = 0.091), and sadness after performance of the task ($\chi^2_{df=2}$ = 4.63, p = 0.099, see Figure 10-9). Importantly, the groups did not differ in other, for the interpretation and/or validity of the results important items. For example, they did not differ in their reported ability to distinguish the colors grey and white; they perceived the task as similarly difficult, and indicated similar ability to stay focused. In line with self-reports, patient and control groups performed equally well in terms of money won in the task (see chapter 5.2.1). Finally, all diagnostic groups rated money as similarly incentive.

6.3.2 Homogeneity of Variance and Distribution of data

Kolmogorov-Smirnov goodness-of-fit tests indicated normal distribution for the majority of variables analyzed except for some characteristics of antisaccade direction errors and their corrective gazes, in particular for controls (see Table 9-5). For the dependant variables of the outcome notification period, Kolmogorov-Smirnov goodness-of-fit tests indicated throughout normal distribution (see Table 9-6). For those variables for which no normal distribution of data could be assumed, non-parametric post-hoc tests were applied to follow up significant interactions of the Analysis of Variance.

Levene tests for homogeneity of variance indicated inhomogeneous variances for peak velocity of different saccadic responses, for percent correct prosaccades, for duration of correct responses, for amplitude of direction errors, and for percent corrective gazes (see Table 9-7). For the outcome notification period, all variables analyzed except for fixation duration after receiving feedback during the reward condition and pupil dilation after positive and combined (i.e. positive and negative) feedback during the neutral condition had homogenous variances (Table 9-8). For variables with inhomogeneous variances, significance level was lowered to 0.025 in the Analysis of Variance.

6.3.3 Significant main effects and interactions performance period

Significant main effects and interactions of the Analysis of Variance will be outlined per between and within subject's factors in the following sections. For an overview of all effects and interactions, see Table 9-15, for an overview of effects and interaction when excluding patients with a comorbid anxiety disorders from the MDD group, see Table 9-16. All post-hoc within-group tests mentioned below are summarized in Table 9-17, results of post-hoc between-group tests in Table 9-18, and descriptives in Table 9-3.

6.3.3.1 Diagnosis-related differences in task performance

There were no significant main effects of **diagnosis** or **type-by-diagnosis** interactions; but several significant **incentives-by-diagnosis** and **incentives-by-type-by-diagnosis** interactions, indicating that the three adolescent groups did not differ in performance of different types of saccadic eye movements per se, but in their modulation of saccadic eye movements by incentives.

6.3.3.2 Incentive-related modulation of task performance

6.3.3.2.1 Effect of Incentives on global performance measures

The three incentive conditions exerted a strong modulatory influence on global task performance as indicated by a significant main effect of **incentives** for *percent correct saccades* ($F_{2,56} = 7.24$, $p \leq 0.05$, $\acute{\eta}_p^2 = 0.21$), which in addition depended on saccade **type** ($F_{2,56} = 7.20$, $p \leq 0.05$, $\acute{\eta}_p^2 = 0.20$) and **diagnostic status** ($F_{2,57} = 3.34$, $p \leq 0.05$, $\acute{\eta}_p^2 = 0.10$), and a significant main effect of **incentives** for *percent antisaccade direction errors* ($F_{2,55} = 3.24$, $p \leq 0.05$, $\acute{\eta}_p^2 = 0.10$).

In terms of *percent correct responses* and *percent antisaccade direction errors*, a series of post-hoc paired-sample t-tests and examination of descriptives and graphs (see Figure 10-10) indicated that while for *percent correct prosaccades* subjects across groups performed best on the reward (33.11 ± 2.13%) and worst on the punishment (30.90 ± 2.97%) condition relative to the other two conditions (neutral condition: 32.01 ± 2.65%; reward – punishment: $T_{66} = 4.35$, $p < 0.017$, $d_z = 0.53$; reward – neutral $T_{66} = 2.89$, $p < 0.017$, $d_z = 0.35$; punishment – neutral: $T_{66} = -2.55$, $p < 0.017$, $d_z = -0.31$), they performed equally well on both contingent conditions for *percent correct antisaccades* (reward condition: 21.65 ± 5.96%, punishment condition: 22.01 ± 7.92%; reward – punishment: $T_{66} = -0.43$, $p = 0.333$) respectively *percent antisaccade direction errors* (reward condition: 11.74 ± 6.26%, punishment condition: 11.58 ± 7.53%; reward – punishment: $T_{66} = 0.12$, $p = 0.417$), with performance on both contingent conditions being superior to that on the neutral condition (correct antisaccades neutral condition: 18.90 ± 8.00%; reward – neutral: $T_{66} = 3.63$, $p < 0.017$, $d_z = 0.44$; punishment – neutral: $T_{66} = 3.72$, $p < 0.017$, $d_z = 0.45$; direction errors neutral condition: 14.12 ± 7.73%; reward – neutral: $T_{66} = -3.35$, $p < 0.017$, $d = -0.41$, punishment – neutral: $T_{66} = -3.47$, $p < 0.017$, $d = -0.42$).

Post-hoc-paired-sample t-tests performed for each subject group separately indicated that the superior performance on the reward condition relative to the neutral or punishment conditions for *percent correct prosaccades* was in particular characteristic for the performance pattern of the control group (reward condition: 32.91 ± 2.10%; punishment condition 30.97 ± 3.17%; neutral condition: 31.51 ± 3.22%; reward – neutral: $T_{31} = 2.50$, $p < 0.017$, $d_z = 0.44$; reward – punishment: $T_{31} = 3.00$, $p < 0.017$, $d_z = 0.53$; punishment – neutral: $T_{31} = -0.87$, $p = 0.195$), while the deterioration of prosaccade performance observed on the punishment condition relative to the reward and neutral conditions was mainly brought about by the MDD group (reward condition: 32.91 ± 1.87%; punishment condition: 30.23 ± 3.65%; neutral condition: 32.82 ± 1.77%; reward – neutral: $T_{11} = 0.11$, $p = 0.457$; reward – punishment: $T_{11} = 1.80$, $p \leq 0.05$, $d_z = 0.52$; punishment – neutral: $T_{11} = -2.50$, $p < 0.017$, $d_z = -0.72$). Finally, anxious patients showed both types of performance patterns observed for either the control or MDD group, i.e. better performance on the reward condition (33.65 ± 2.38%) relative to the neutral (32.39 ± 1.56%) and punishment (31.29 ± 1.89%) conditions and a trend for deterioration of performance on the punishment relative to the neutral condition (reward – neutral: $T_{15} = 1.84$, $0.017 \leq p \leq 0.05$, $d_z = 0.46$; reward – punishment: $T_{15} = 2.56$, $p < 0.017$, $d_z = 0.64$; punishment – neutral: $T_{15} = -1.56$, $0.05 \leq p \leq 0.10$, $d_z = -0.39$). For *correct antisaccades* and *antisaccade direction errors*, post-hoc paired-sample t-tests indicated that the above reported better performance on both contingent conditions relative to the neutral condition persisted for controls only (*correct antisaccades*: reward condition: 22.25 ± 5.32%; punishment condition: 23.15 ± 8.11%; neutral condition: 18.41 ± 7.91%; reward – neutral: $T_{31} = 3.40$, $p < 0.017$, $d_z = 0.60$; punishment – neutral: $T_{31} = 4.10$, $p < 0.017$, $d_z = 0.72$; *antisaccade direction errors*: reward condition: 11.05 ± 5.62%; punishment condition: 10.67 ± 7.64%; neutral condition: 14.48 ± 7.77%; reward – neutral: $T_{31} = -3.09$, $p < 0.017$, $d_z = -0.55$; punishment – neutral: $T_{31} = -3.41$, $p < 0.017$, $d_z = -0.60$), while both patient groups did not show a significant modulation of correct antisaccades by incentives. A series of independent-sample t-tests revealed no significant differences between any two of the three diagnostic groups on any of the single incentive conditions of either *percent correct prosaccades*, *correct antisaccades*, or *antisaccade direction errors*.

In terms of *percent corrective saccades*, it was hypothesized that greater sensitivity for punishments in patients with anxiety may be reflected in a higher proportion of direction errors during this condition being corrected as compared to the other incentive conditions (see chapter 4). This hypothesis was supported by exploratory paired-sample t-tests performed for each diagnostic group and examination of descriptives and graphs (see Figure 10-10): Specifically, while controls did not show differences between any two of the three incentive conditions for percent corrective saccades, patients with anxiety corrected more antisaccade direction errors that occurred on the punishment (88.57 ± 12.38%) than neutral condition (75.10 ± 27.62%; $T_{16} = 2.18$, $0.017 \leq p \leq 0.05$, $d_z = 0.55$). In contrast, patients with MDD showed a trend for correcting more antisaccade direction errors on the neutral condition (86.04 ± 19.03) as compared to the punishment condition (78.53 ± 22.24%; $T_{11} = -1.50$, $0.05 \leq p \leq 0.10$, $d_z = -0.43$). Accordingly, independent sample t-tests indicated that patients with anxiety corrected more errors on the punishment condition than did controls (74.48 ± 24.53%; $T_{46} = -2.62$, $p \leq 0.05$, $d = -0.73$) and on a trend level but with satisfactory effect size than patients with MDD ($T_{16.41} =$

1.41, 0.05 ≤ p ≤ 0.10, d = 0.56), while patients with MDD corrected significantly more antisaccade direction errors on the neutral condition as compared to controls (70.17 ± 27.18; T_{42} = -1.85, p ≤ 0.05, d = -0.68).

6.3.3.2.2 Effect of Incentives on dynamic performance measures

As revealed by Analysis of Variance, incentives modulated with exception of saccade duration all dynamic saccade parameters investigated such as saccadic reaction times, saccade peak velocities and saccade amplitudes. In addition, for all of these dynamic saccade characteristics, modulation differed between groups per saccade type, indicating that cognitive control was differently affected by incentives in the three diagnostic groups. Moreover, interactions between diagnostic group and incentives became more significant when excluding patients with comorbid anxiety disorders from the MDD group.

Reaction Time Measures

In terms of saccadic reaction times, there was a significant main effect of **incentives** for *latency of correct saccades* ($F_{2,56}$ = 3.59, p ≤ 0.05, $ή_p^2$ = 0.11), which differed between **diagnostic groups** ($F_{2,57}$ = 3.14, p = 0.05, $ή_p^2$ = 0.10), saccade **type** ($F_{2,56}$ = 3.58, p ≤ 0.05, $ή_p^2$ = 0.11) and finally between **diagnostic groups** and saccade **type** ($F_{2,57}$ = 4.13, p ≤ 0.05, $ή_p^2$ = 0.13). In addition, there was a significant main effect of **incentives** for *latency of corrective saccades* ($F_{2,51}$ = 3.50, p ≤ 0.05, $ή_p^2$ = 0.12).

In terms of *latency of correct responses*, paired-sample t-tests conducted per saccade type and diagnostic group revealed that neither patient group showed a significant modulation of these measures (see also Figure 10-10). In contrast, controls modulated saccade latency by incentives, but only during visually-guided saccades, i.e prosaccades, but not during internally-guided antisaccades. Specifically, controls *initiated correct prosaccades* significantly later on the punishment condition (192.06 ± 30.91ms) as compared to the reward condition (186.16 ± 26.71ms; T_{31} = -2.42, p < 0.017, d_z = -0.43). This pattern of modulation was corroborated by exploratory examination of antisaccade direction errors (see also developmental study, chapter 6.2.3.2.2), which also can be considered visually-guided saccades. Here, controls *initiated antisaccade direction errors* significantly later on the reward condition (206.79 ± 59.22ms) as compared to the neutral condition (183.73 ± 36.58ms; T_{31} = 2.43, p < 0.017, d_z = 0.43).

Independent-sample t-tests revealed significant differences in latency of primary saccades (i.e. correct pro- and antisaccades, and antisaccade direction error) between groups for several incentive conditions. Specifically, patients with MDD *initiated correct antisaccades* earlier on the punishment condition (patients with MDD: 247.87 ± 88.37ms; controls: 293.67 ± 51.89ms; T_{42} = 2.13, p ≤ 0.05, d = 0.63) and *antisaccade direction errors* faster on the reward condition (patients with MDD: 175.26 ± 30.47ms; controls: 206.79 ± 59.22ms; T_{42} = 1.75, p ≤ 0.05, d = 0.67) as compared to controls. Patients

with anxiety initiated saccades of both saccade types generally faster than did controls across conditions (see Figure 10-10). This resulted in trends for group differences between anxious patients and controls for *correct prosaccades* on the reward condition (patients with anxiety: 174.89 ± 26.12ms; controls: 186.16 ± 26.71ms; $T_{46} = 1.39$, $0.05 \leq p \leq 0.10$, $d = 0.43$) and punishment condition (patients with anxiety: 178.16 ± 22.32ms; controls: 192.06 ± 30.91ms; $T_{46} = 1.60$, $0.05 \leq p \leq 0.10$, $d = 0.52$).

In terms of *latency of corrective saccades*, paired-sample t-tests performed across subjects indicated that corrective saccades were initiated faster on the reward condition (185.97 ± 113.58ms) relative to the neutral condition (246.77 ± 149.51ms; $T_{66} = -2.23$, $p < 0.017$, $d_z = -0.29$) and on a trend level relative to the punishment condition (229.21 ± 155.82ms; $T_{66} = -1.77$, $0.017 \leq p \leq 0.05$, $d_z = -0.23$). Paired-sample t-tests conducted per diagnostic group indicated that the delay of initiation of corrective saccades on the punishment condition relative to the reward condition was brought about by the two patients groups (patients with MDD, reward condition:190.74 ± 110.74ms; punishment condition: 269.01 ± 140.72ms; $T_{11} = -1.62$, $0.017 \leq p \leq 0.10$, $d_z = -0.47$; patients with anxiety, reward condition: 158.62 ± 120.49ms; punishment condition: 236.54 ± 177.70ms; $T_{15} = -1.72$, $0.017 \leq p \leq 0.10$, $d_z = -0.43$), while the delay of initiation on neutral trials relative to the two contingent conditions was more characteristic for the response pattern observed for the control group (reward condition: 198.65 ± 112.27ms; punishment condition: 209.39 ± 150.95ms; neutral condition: 280.85 ± 154.47ms; reward – neutral: $T_{28} = -3.12$, $p < 0.017$, $d_z = -0.58$; punishment – neutral: $T_{28} = -1.76$, $0.017 \leq p \leq 0.05$, $d_z = -0.33$). Independent sample-tests did not show significant differences between groups for latency of corrective saccades on any of the three incentive conditions. However, there was a trend for controls to initiate corrective saccades later on the neutral condition (280.85 ± 154.47) as compared to patients with anxiety (204.21 ± 13.93ms; $T_{44} = 1.61$, $0.05 \leq p \leq 0.10$, $d = 0.56$).

Saccade Peak Velocity

For peak velocity, there was a trend for a **incentives-by-type-by-diagnosis** interaction for *peak velocity of correct responses* ($F_{2,57} = 3.33$, $0.025 \leq p \leq 0.05$, $\acute{\eta}_p^2 = 0.10$) and a trend for a **incentives-by-diagnosis** interaction for *peak velocity of antisaccade direction errors* ($F_{2,56} = 2.70$, $0.05 \leq p \leq 0.10$, $\acute{\eta}_p^2 = 0.09$). Both trends were followed up being of interest for the hypotheses of this thesis. In addition, when excluding the four subjects with comorbid anxiety disorder from the MDD group, the trend for an interaction between incentives and diagnostic group reached significance level for peak velocity of correct responses, and became stronger for peak velocity of antisaccade direction errors.

Post-hoc paired-sample t-tests and examination of descriptives and graphs (see Figure 10-10) per subject group and saccade type indicated that while controls modulated *peak velocity of correct prosaccades* and *peak velocity of antisaccade direction errors* by incentives, both clinical groups failed to show an incentive-related modulation for any of the dependant variables analyzed that would reach significance level. For the control group, *prosaccade peak velocities* were significantly faster on the punishment condition (92.94 ± 13.26° visual angle/s) as compared to the neutral condition (88.62 ± 11.03° visual angle/s; $T_{31} = 2.65$, $p < 0.017$, $d_z = 0.47$). In addition, the control group had significantly

faster *peak velocities of antisaccade direction errors* on the reward (104.37 ± 48.60° visual angle/s) relative to the neutral condition (82.49 ± 10.46° visual angle/s; $Z = -2.15$, $p < 0.017$, $d_z = 0.49$).

Independent-sample t-tests indicated differences between the control and anxious group, but not between the control and the MDD group or between the two patient groups. Specifically patients with anxiety had high *peak velocity for correct responses of both saccade types*, regardless of incentive condition. This resulted in group differences to controls on the neutral condition for correct antisaccades (patients with anxiety: 114.68 ± 23.72° visual angle/s; controls: 102.40 ± 23.99° visual angle/s; $T_{46} = -1.68$, $p \leq 0.05$, $d = -0.51$) and on a trend level for correct prosaccades (patients with anxiety: 94.46 ± 14.97° visual angle/s; controls: 88.62 ± 11.03° visual angle/s; $T_{46} = -1.53$, $0.05 \leq p \leq 0.10$, $d = -0.44$).

Saccade Amplitude

For *amplitudes of correct responses*, there were trends for an interaction of **incentives-by-diagnosis** ($F_{2,57} = 3.67$, $0.025 \leq p \leq 0.05$, $\acute{\eta}_p^2 = 0.12$) and **incentives-by-type-by-diagnosis** ($F_{2,57} = 3.91$, $0.025 \leq p \leq 0.05$, $\acute{\eta}_p^2 = 0.12$) interactions.

Post-hoc paired-sample t-tests per saccade type and group and examination of descriptives and graphs (see Figure 10-10) indicated similarly to reaction time measures and peak velocity, that while both patient groups did not show a significant incentive-related modulation of saccade amplitude of neither correct pro- or antisaccades, controls had significantly larger *amplitude of correct prosaccades* on the reward condition (4.99 ± 0.39° visual angle) as compared to the neutral condition (4.86 ± 0.39° visual angle; $T_{31} = 2.88$, $p < 0.017$, $d_z = 0.51$).

Independent-sample t-tests revealed group differences between patients with MDD and controls for *amplitude of correct antisaccades* on the punishment condition ($T_{42} = -1.88$, $p \leq 0.05$, $d = -0.55$) and for *amplitude of correct prosaccades* on all incentive conditions (punishment: $T_{42} = -2.01$, $p \leq 0.05$, $d = -0.62$; reward: $T_{42} = -1.96$, $p \leq 0.05$, $d = -0.60$; neutral: $T_{42} = -1.83$, $p \leq 0.05$, $d = -0.56$), with patients with MDD having consistently larger amplitudes than controls (*amplitude of correct antisaccades* punishment condition, patients with MDD: 7.03 ± 2.45° visual angle; controls: 5.92 ± 1.42° visual angle; *amplitude of correct prosaccades*, patients with MDD: reward condition: 5.28 ± 0.56° visual angle, punishment condition: 5.30 ± 0.68° visual angle; neutral condition: 5.13 ± 0.56° visual angle; controls: reward condition: 4.99 ± 0.39° visual angle, punishment condition: 4.94 ± 0.47° visual angle; neutral condition: 4.86 ± 0.39° visual angle). Patients with an anxiety disorder similarly to patients with MDD had large amplitudes for all incentive conditions, differing from controls for correct prosaccades on the neutral condition (patients with anxiety: 5.11 ± 0.39° visual angle; controls: 4.86 ± 0.39° visual angle; $T_{46} = -2.04$, $p \leq 0.05$, $d = -0.61$). The two patient groups did not differ significantly from each other on any incentive condition for amplitudes of correct pro- or antisaccades.

6.3.3.3 Saccade type related differences in task performance

Similarly to the developmental study, correct prosaccades and correct antisaccades differed on all characteristics investigated, indicating that the different types of saccades recruited different cognitive functions and underlying substrates across subjects regardless of clinical state. Specifically, there were more correct pro- than antisaccades per incentive condition (32.01 ± 2.58% vs. 20.85 ± 7.30%; $F_{1,57}$ = 157.19, p ≤ 0.05, $ή_p^2$ = 0.73), correct antisaccades were initiated later than correct prosaccades (286.73 ± 54.48ms vs. 184.38 ± 30.51ms; $F_{1,57}$ = 440.75, p ≤ 0.05, $ή_p^2$ = 0.89), had faster peak velocities than prosaccades (109.26 ± 32.38° visual angle/s vs. 91.59 ± 11.49° visual angle/s; $F_{1,57}$ = 38.46, p ≤ 0.025, $ή_p^2$ = 0.40), longer durations (119.14 ± 23.30ms vs. 106.45 ± 9.33ms; $F_{1,57}$ = 26.10, p ≤ 0.025, $ή_p^2$ = 0.31), and larger saccade amplitudes (6.31 ± 1.68° visual angle vs. 5.04 ± 0.48° visual angle; $F_{1,57}$ = 45.76, p ≤ 0.05, $ή_p^2$ = 0.45).

6.3.4 Significant main effects and interactions outcome notification period

Significant main effects and interactions of the Analysis of Variance will be outlined per dependant variable in the subsequent sections. For an overview of significant effects and interactions, see Table 9-19, for an overview of descriptives per age group, see Table 9-4.

6.3.4.1 Fixation Duration

Duration of the first fixation after feedback onset differed between **feedback** type across subjects ($F_{1,57}$ = 6.49, p ≤ 0.05, $ή_p^2$ = 0.10) with fixation duration being longer for positive feedback (0.54 ± 0.11s) as compared to negative feedback (0.49 ± 0.08s) across diagnostic groups (see Figure 10-11).

In addition, *duration of the first fixation after feedback onset* differed on a trend level with satisfactory effect size between **diagnostic** groups by **feedback** type and **incentive** condition ($F_{2,57}$ = 3.11, 0.05 ≤ p ≤ 0.10, $ή_p^2$ = 0.10). Post-hoc paired-sample t-tests per diagnostic group, incentive condition and feedback type indicated that while controls and patients with anxiety disorders did not modulate fixation duration by incentives for neither type of feedback, patients with MDD modulated fixation duration differently between incentive conditions for negative feedback. In particular, patients with MDD fixated negative feedback longer on the punishment condition (0.63 ± 0.22) as compared to the neutral condition (0.49 ± 0.17s; T_{11} = 2.93, p < 0.017, d_z = 0.84) and on a trend level as compared to the reward condition (0.50 ± 0.18s; T_{11} = -1.94, 0.017 ≤ p ≤ 0.05, d_z = -0.56). This prolongation of fixation duration on the punishment condition for negative feedback in the MDD group lead to a significant difference to the other two diagnostic groups for this measure (controls: 0.51 ± 0.16s, patients with anxiety: 0.48 ± 0.14s; controls – patients with MDD: T_{42} = -1.94, p ≤ 0.05, d = -0.62, patients with MDD – patients with Anxiety: T_{26} = -2.13, p ≤ 0.05, d = -0.81). On a trend level, patients with MDD also had

longer fixation duration for positive feedback as compared to controls on the punishment condition (patients with MDD: 0.57 ± 0.11s; controls: 0.52 ± 0.10s; T_{42} = -1.46, 0.017 ≤ p ≤ 0.10, d = -0.48). There were no other differences between any two of the three diagnostic groups for any other incentive condition for duration of the first fixation after feedback onset.

6.3.4.2 Pupil diameter

Pupil diameter during the first fixation after feedback onset differed significantly between **feedback** type ($F_{1,57}$ = 80.63, p ≤ 0.05, $\acute{\eta}_p^2$ = 0.59), with subjects across diagnostic groups having larger pupil diameter for negative (7.05 ± 1.30mm) than positive feedback (6.90 ± 1.34mm) (see also Figure 10-11). In addition, *pupil diameter during the first fixation after feedback onset* differed between **incentive** conditions ($F_{2,56}$ = 10.68, p ≤ 0.05, $\acute{\eta}_p^2$ = 0.28) and on a trend level between **diagnostic** groups ($F_{2,57}$ = 2.87, 0.05 ≤ p ≤ 0.10, $\acute{\eta}_p^2$ = 0.09). Post-hoc paired-sample t-tests per incentive condition indicated that subjects across diagnostic groups had greater pupil diameter for the two incentive conditions (reward condition: 7.00 ± 1.31mm, punishment condition: 6.99 ± 1.33mm) as compared to the neutral condition (6.93 ± 1.31mm; reward – neutral: T_{66} = 5.41, p < 0.017, d_z = 0.66, punishment – neutral: T_{66} = 4.44, p < 0.017, d_z = 0.54). Finally post-hoc Scheffé tests indicated a trend for a significant difference between patients with MDD and controls for pupil diameter, with patients with MDD having overall smaller pupil diameter (6.34 ± 0.94mm) than controls (7.32 ± 1.53mm, 0.05 ≤ p ≤ 0.10), but not as compared to patients with Anxiety (6.76 ± 0.86mm, p = 0.372).

6.3.4.3 Pupil Dilation

Pupil dilation differed between **feedback** type ($F_{1,57}$ = 26.38, p ≤ 0.025, $\acute{\eta}_p^2$ = 0.32), which additionally was modulated by **incentive** condition ($F_{2,56}$ = 6.27, p ≤ 0.025, $\acute{\eta}_p^2$ = 0.18). Examination of descriptives and graphs (see Figure 10-11) indicated that across subjects of all diagnostic groups, pupil diameter dilated after notification of negative outcome (0.028 ± 0.080mm) whereas for positive feedback, there was a constriction in pupil diameter (-0.012 ± 0.069mm). Post-hoc paired-sample t-tests between different incentive conditions per feedback type indicated that while for negative feedback pupil dilation was significantly greater for the reward (0.043 ± 0.090) as compared to the neutral condition (0.013 ± 0.070; reward – neutral: T_{66} = 2.44, p < 0.017, d_z = 0.30), for positive feedback dilation was greater for the punishment condition (-0.022 ± 0.076) as compared to the reward condition (-0.010 ± 0.069; T_{66} = 2.20, p < 0.017, d_z = 0.27) and on a trend level as compared to the neutral condition (-0.004 ± 0.061mm; T_{66} = -1.89, 0.017 ≤ p ≤ 0.05, d_z = 0.23).

7. Discussion

The current study investigated developmental and clinical differences in performance on a Reward Saccade Task (RST) in which saccadic eye movements of differing cognitive demand were to be performed under a contingency schedule. Specifically, subjects had to perform in random fashion either a prosaccade, which is a saccadic eye movement towards a target appearing in the peripheral visual field, or an antisaccade, which is a saccadic eye movement towards the mirror location of the target, and depending on performance accuracy they could either win or not win 1$ (“reward” condition), lose or not lose 1$ (“punishment” condition), or did receive performance feedback without monetary implications (“neutral” condition). While prosaccades are externally, visually-guided eye movements that principally rely on visual attention and sensori-motor processes, antisaccades are internally guided, voluntary eye movements which rely on inhibitory processes in addition to the same processes engaged in prosaccades (attention and sensori-motor systems). Moreover, the structure of the RST introduces an additional cognitive load in the form of working memory (remember the significance of the saccadic instruction cue, i.e., grey color of the cue signaling an antisaccade trial, and white color signaling a prosaccade trial).

Two stages of the RST were investigated, the actual performance period, and the outcome notification period, from two perspectives, a developmental perspective comparing performance of healthy adolescents and adults, and a clinical perspective comparing performance of healthy adolescents with a sample of adolescents with clinical depression and a sample of adolescents with an anxiety disorder. The task performance period was characterized by five parameters: accuracy of saccadic responses, saccade latency, saccade peak velocity, saccade duration and saccade amplitude. While accuracy provides a more global index of performance, saccade latency, peak velocity, duration and amplitude index dynamic characteristics of eye movement preparation (latency) and regulation (peak velocity, duration and amplitude). Moreover, all saccadic parameters employed can be mapped onto specific neural circuits and thus can be used as an index of the function of these circuits in different populations. Reaction to feedback presentation was measured by three parameters: Pupil diameter, pupil dilation, and duration of the fist fixation after feedback onset. Findings of the developmental study (see chapter 6.2) and the clinical study (see chapter 6.3) are discussed separately.

7.1 Developmental study

For the developmental aspect of this study, it was hypothesized that 1) adults will outperform adolescents on antisaccade trials because of the still ongoing maturation of prefrontal cortex networks and cognitive control functions during adolescence, that 2) the prospect of monetary reward will improve task performance across groups, that 3) incentives (i.e. prospect of winning or losing money as compared to no monetary implication) will influence task performance in adolescents more strongly than in adults, in particular under conditions of comparatively low cognitive control (i.e. weaker incen-

tive-related modulation of correct antisaccades as compared to antisaccade direction errors and prosaccades), and 4) that adolescents will be less affected than adults by negative performance feedback. The findings largely support these hypotheses, specifically, 1) cognitive control was superior in adults than adolescents as indicated by a higher rate of correct antisaccades and earlier initiation of correct antisaccades in adults as compared to adolescents, 2) the prospect of winning money improved global accuracy on the task in both adults and adolescents; 3) adolescents but not adults showed an incentive-related modulation of the dynamic characteristics of saccadic eye movements, selectively in the context of prosaccades and antisaccade direction errors; and 4) outcome notification lead to greater change in eye movement parameters in adults as compared to adolescents. Results are discussed in more detail by hypothesis in the sections below.

7.1.1 Age-related differences in RST performance

As hypothesized, performance on the RST improved with age: Adults performed better than adolescents on antisaccade trials as indicated by a higher proportion of correct antisaccades respectively a lower proportion of antisaccade direction errors. In contrast, performance on prosaccade trials did not differ significantly between age groups. The lack of a group difference on prosaccade trials suggests that the overall efficiency of visually-guided eye movements has reached maturity by adolescence, in line with other developmental research showing adult level performance on prosaccades by middle to late childhood (e.g. Fischer, Gezeck et al., 1997; Fukushima et al., 2000; C. Klein & Foerster, 2001; Munoz et al., 1998). It also suggests that the additional cognitive load of working memory of the RST (remembering which cue asks for which saccadic response) did not affect adolescents and adults differentially during preparation and initiation of a saccade and thus is not a main reason for the differences observed in antisaccade performance between age groups. Rather, the worse antisaccade performance of adolescents as compared to adults indicates that the cognitive capacities and the neural circuits specifically underlying antisaccade performance have not reached maturity by adolescence.

In terms of the neural substrates underlying antisaccade performance, clinical and translational animal research point towards a central role of the dorsolateral prefrontal cortex (DLPFC) in determining antisaccade performance accuracy (for review see Broerse et al., 2001; Everling & Fischer, 1998; Hutton & Ettinger, 2006; Munoz & Everling, 2004) (see chapter 3.2.1.1). For example, transcranial magnetic stimulation applied over the DLPFC 100ms before target onset significantly increases antisaccade error rate (Nyffeler et al., 2007), and patients with lesions of the DLPFC but not the parietal cortex show increased error rates on the antisaccade task (for review see Gaymard et al., 1998; Milea et al., 2005; Pierrot-Deseilligny et al., 2002; Sweeney et al., 2002). The higher number of incorrect responses on antisaccade trials in adolescents as compared to adults thus points to immature prefrontal cortex function in youth, in line with other developmental research showing protracted development of the (dorsolateral) prefrontal cortex up until late adolescence/early adulthood (Giedd, 2004; Giedd et al., 2006) (see chapter 2.1) and in line with eye movement research showing adult

performance level on the antisaccade task not before late adolescence (Fischer, Biscaldi et al., 1997; Fukushima et al., 2000; Kramer et al., 2005; Luna et al., 2001) (see chapter 3.3).

In terms of the cognitive capacities underlying antisaccade performance, two main processes are proposed to be involved: (1) inhibition of the natural tendency to look at a suddenly appearing target, and (2) generation of a saccade in absence of visual input towards the mirror position of the target (for review see Broerse et al., 2001; Everling & Fischer, 1998; Hallett & Adams, 1980; Hutton & Ettinger, 2006; Munoz & Everling, 2004) (see chapter 3.1). A low proportion of correct antisaccades *in conjunction with* an increased proportion of antisaccade direction errors commonly have been interpreted as a failure to inhibit prepotent, reflexive responses. In contrast, a low proportion of correct antisaccades *in absence* of increased numbers of antisaccade direction errors commonly have been used as an index for a failure to generate an internally-guided behavior. In addition, the rate of corrective saccades after an antisaccade direction error may be used as an index of the ability to generate an internally-guided movement and serve as a proof of task comprehension (e.g. Everling, Dorris et al., 1998; Munoz & Everling, 2004). Thus, the results obtained here - increased error rates in adolescents as compared to adults and no difference between age groups in the proportion of correct prosaccades and the proportion of corrective saccades - indicate that the worse performance of adolescents on antisaccade trials was not because they could not generate internally-guided voluntary behavior, neither in age-related differences in working memory capacities or task understanding, but mainly because of an impairment in inhibiting prepotent, reflexive responses.

Yet, although adolescents were able to perform correct antisaccades per se and corrected their direction errors as often as did adults, they did so with significantly greater latency than adults. This finding further specifies the above conclusions indicating that although functional and in place, internally-guided programming of behavior nevertheless affords more time and cognitive capacity in adolescents as compared to adults. Latency of internally-guided saccades has been shown in non-human primate studies to reflect the pre-target activity and/or the rate of rise in the post-target activity of neurons in the supplementary eye fields (SEF) and the frontal eye fields (FEF) located anterior of the motor cortex in the frontal lobe (for review see Munoz & Everling, 2004) (see Figure 3-3 and chapter 3.2.1.2). In addition, there is evidence indicating that the rise of activity in the SEF can be modulated by the goal of a task (Stuphorn & Schall, 2006). Thus, longer latency of antisaccades and corrective saccades in the current context may reflect a slower accumulation of neuronal activity in the SEF and/or FEF brought about by lower efficiency of goal-related network activity in the frontal cortex in adolescents as compared to adults. Similar conclusions have been drawn by Luna et al. (2001), who by means of fMRI reported greater activation in adolescents as compared to adults in the DLPFC and inferior FEF during performance of an antisaccade task, while adults showed increased activity in posterior cortical and subcortical brain regions. The authors interpreted these findings as indicating incomplete integration of neural networks orchestrated by the PFC at adolescence, requiring greater effort to exert cognitive control over reflexive behaviors as compared to adults (on similar fMRI reports, see chapter 2.1.2). Of note, similarly to the finding of increased error rates during the antisaccade task, also the finding of increased latencies of internally-guided saccades is in line with other devel-

opmental research on the antisaccade task, reporting adult level in antisaccade latency and latency of corrective saccades not before late adolescence or even early adulthood (e.g. Fischer, Biscaldi et al., 1997; Munoz et al., 1998) (see chapter 3.3).

Finally, adolescents had significantly higher peak velocities than adults on correct antisaccades. In contrast to the results discussed above about increased antisaccade error rates and latency in youth, this finding contradicts other developmental research on antisaccade task performance. To my knowledge, two studies to date have compared antisaccade peak velocity between adolescents and adults and both of them report no differences between age groups on this measure (Fukushima et al., 2000; Luna et al., 2001). Both research groups explain the dissociation in the development of antisaccade latency (improvement during childhood and adolescence) and antisaccade peak velocity (no developmental improvement) by the maturational lags of the different neural circuits supporting the two functions. Saccade latency, which involves processes before initiation of a saccade, has been shown to be modulated by activity of frontal brain areas as reported above. Peak velocity, which involves processes of motor regulation, has been proposed to depend on subcortical brain circuits in the brainstem and cerebellum (for review see Leigh & Kennard, 2004) (see chapter 3.2.1.3) - circuits that are largely developed by early-middle childhood (Fukushima et al., 2000). However, other findings indicate that peak velocity can be modulated by activity of prefrontal and/or basal ganglia projections to the saccade generation network in the brainstem (see also Figure 3-3 in chapter 3.2). For example, stimulation of the SEF increases peak velocity of anticipatory smooth pursuit eye movements (Missal & Heinen, 2001). In contrast, reductions of saccade peak velocity have been observed after inactivation of the FEF produced by injection of lidocaine (Sommer & Tehovnik, 1997) or the $GABA_A$ agonist muscimol (Dias & Segraves, 1999) and after medication with neuroleptics (Fukushima et al., 2000; Straube, Riedel, Eggert, & Muller, 1999). Straube et al. (1999) for example have reported significantly reduced peak velocity of internally-guided saccades (i.e. antisaccades or memory-guided saccades) but not externally-guided saccades (i.e. prosaccades) in patients medicated with neuroleptics as compared to their pre-medication state and as compared to controls. An increase in peak velocity of internally-guided saccades has also been reported in non-human primates under the influence of reward, which has been proposed to be mediated through the basal ganglia or prefrontal input to the brainstem saccade generation network (e.g. Kawagoe et al., 1998; Kobayashi et al., 2002; Takikawa, Kawagoe, Itoh et al., 2002) (see chapter 7.1.3). Finally, changes in saccade peak velocity have been observed under influence of anesthetics, leading to the use of this measure as a biophysical index of alertness, and sedation during anesthesia (for review see Khan, Taylor, & Jones, 2000). Thus, the increased peak velocity observed in adolescents as compared to adults in this study may reflect age-related differences in upstream (i.e. prefrontal cortical and/or basal ganglia) modulation of the brainstem saccade generation circuit, brought about by structural differences in these upstream brain areas, higher sensitivity of these brain areas to the reward context in which the task was performed in adolescents as compared to adults, and/or as a result of an increased level of arousal in adolescents as compared to adults. Less likely is that maturational changes in the brainstem itself lead to differences in peak velocity between age groups.

Finally, the age-related differences in RST performance obtained here are consistent with the data published in 2006 that were based on the same task and largely the same subject group (Jazbec et al., 2006), with some exceptions. For example, increased latencies for correct antisaccades in adolescents as compared to adults were also observed in the previous publication, but the group differences did not reach significance. In addition, similarly to the current results, higher peak velocity in adolescents as compared to adults were observed in the Jazbec et al. (2006) study, however group differences reached significance for correct prosaccades and antisaccade direction errors, whereas in the current study, group differences reached significance for correct antisaccades. These differences in results observed between the two studies might be due to several methodological differences, such as number of subjects (in the current study, data of 9 additional adolescents were included), and in terms of differences in data extraction procedures and criteria used. For example, in the Jazbec et al. (2006) study, saccade parameters were extracted from the raw data based on information about fixations, whereas in the current study, saccades were defined independent from information about fixations based on saccade velocity and size, a procedure more commonly used in eye movement research (Fischer, Gezeck et al., 1997).

7.1.2 Incentive-related modulation of RST performance across age groups

As predicted, the prospect of a monetary gain improved accuracy of prosaccades and antisaccades in both age groups, i.e. subjects across age groups had a higher proportion of correct prosaccades and correct antisaccades for the reward condition as compared to the neutral, non-incentive condition. This improvement in task performance was expected based on the neuroscience conceptualization of rewards being anything an organism will put forth effort to obtain (Rolls, 2000) (see chapter 2.2.1.1), and based on results obtained in non-human primates (Kawagoe et al., 1998; Kobayashi et al., 2002; Takikawa, Kawagoe, Itoh et al., 2002) and one human study (Duka & Lupp, 1997) reporting enhanced accuracy of internally-guided eye movements under incentives (see chapter 3.5). Importantly, this improvement by the prospect of monetary gain indicates that the incentive manipulation of the RST exerted its desired influence.

The threat of a monetary loss (punishment condition) also influenced performance accuracy in a similar fashion in adults and adolescents. However, its effect was more complex than that of rewards: It improved accuracy on antisaccade trials, but not on prosaccade trials as compared to the non-incentive, neutral condition. This latter finding is in line with the results published by Jazbec et al. (2006) obtained by a different data preparation procedure and with a smaller sample size. Specifically, in the Jazbec et al. (2006) study, accuracy was determined by the location of the first fixation after target onset, whereas in the current analysis, accuracy was determined by the direction of the first saccade after target onset.

There are two possibilities that may explain lack of improvement of task performance on the punishment condition of prosaccade trials. First, it may reflect *increased attentional engagement with a*

threat-associated stimulus, hampering attention allocation towards a new position and initiation of a saccadic eye movement towards it. Alternatively, it may reflect *avoidance of a threat-related stimulus*, assuming that not only the cue but also the target was associated by subjects with the threat of losing money during the punishment condition. Both possibilities comply with cognitive models and research on emotional biases in information processing in low-anxious individuals, which suggests that stimuli perceived as highly threatening draw increased attentional resources, whereas mildly threatening stimuli are avoided, presumably in an attempt of emotion regulation to preserve a positive mood state (e.g. MacLeod & Mathews, 1988; for review see Mogg & Bradley, 1998; Mogg, Bradley, & Hallowell, 1994). In addition, both possibilities are in line with the finding of improved performance on the punishment condition for correct antisaccades: On one hand, increased attentional engagement with the cue signaling threat allows more time for the voluntary antisaccade away from the target to be programmed, given that programming of a correct antisaccade commonly requires more time that that of visually-guided saccades (for review see Broerse et al., 2001; Fischer, 1999; Hutton & Ettinger, 2006; Munoz & Everling, 2004) (see chapter 3.1.1.2). On the other hand, attention allocation away from a threat-associated stimulus complies with the antisaccade instruction of moving away from the target. Finally, saccade latency was increased on punishment trials for correct responses as compared to the reward and neutral condition across subjects, although reaching within-group significance only for adolescents (see Table 9-11, for discussion of developmental differences in RST performance, see paragraph below). In stimulus-response tasks, increased latency of a response in conjunction with an emotionally salient stimulus commonly has been taken as an index of increased attentional engagement with the stimulus (Mogg & Bradley, 1998, see also paragraph below). Thus, both possibilities - increased attentional engagement with a threat-associated stimulus or avoidance of a threat-related stimulus - may apply to explain deterioration of performance on prosaccade but improvement on antisaccade trials during the punishment condition, the first one possibly affecting more strongly adolescents, the second one adults.

7.1.3 Incentive-related modulation of RST performance: Developmental differences

While global accuracy (percent correct responses – percent direction errors) was modulated by incentives similarly across groups, the dynamic measures of task performance showed a more complex pattern of modulation by incentives with some noticeable differences between age groups. Specifically, while adults did not show significant within-group differences between the three incentive conditions for any dynamic parameter of any primary saccade analyzed (i.e. correct antisaccades, correct prosaccades or antisaccade direction errors, see Table 9-11), adolescents showed a clear modulation of dynamic saccade parameters for correct prosaccades and antisaccade direction errors. For example, adolescents initiated correct prosaccades later and with higher peak velocity when facing the threat of monetary loss as compared to the reward respectively the neutral condition and as compared to adults. In terms of antisaccade direction errors, the same was true for the prospect of winning money, i.e. adolescents initiated antisaccade direction errors later for the reward condition and

with higher peak velocity than for the other incentive conditions and as compared to adults. In contrast, adults but not adolescents showed a more pronounced modulation of corrective saccades, i.e. for saccades initiated after an antisaccade direction error.

As mentioned above, increased reaction times in conjunction with emotionally salient stimuli such as threats may indicate increased capture of attention by these stimuli. For example, in the emotional Stroop color-naming task, in which subjects have to name the color in which words with emotional contents are printed, increased color-naming latency commonly is interpreted as reflecting the extent to which attentional resources are engaged by the emotional content of the word (Mogg & Bradley, 1998). Thus, more time needed to program and initiate a simple, visually-guided prosaccade in adolescents during the punishment condition as compared to the other conditions and as compared to adults might indicate that the prospect of a monetary loss engaged more attentional resources in adolescents as compared to adults. Alternatively or in parallel, more time needed to program and initiate a simple visually-guided eye movement under the punishment condition may indicate that adolescents were more strongly disrupted by the prospect of a monetary loss than adults. Evidence supporting this notion is the deterioration of global performance (for discussion see chapter 7.1.2 above) and the increased peak velocities of adolescents for correct prosaccades under the punishment condition, given that peak velocity serves as an indicator of arousal (for review see Khan et al., 2000) (see also chapter 7.1.1). Finally, a dissociation of prosaccade performance on the two incentive conditions in adolescents, with delayed initiation and deterioration of performance on the punishment condition, but efficient initiation and improved performance for the reward condition, points towards a conflict between motivational and cognitive demands of the task in youth: During the prosaccade instruction, gazing at the target under the reward condition is congruent with the motivation to approach a reward, while for the punishment condition, the cognitive demand to gaze at the target contradicts the natural motivation to avoid a threat-associated stimulus. Thus, all of these scenarios alone or in combination essentially imply that adolescents were more strongly affected in performance of a simple visually-guided eye movement by the threat of a monetary punishment as were adults.

A higher conflict between motivational and cognitive aspects of task performance in adolescents as compared to adults also offers a readily explanation for the increased latency and peak velocity observed in adolescents for antisaccade direction errors under the reward condition. That is, more time to initiate an (incorrect) eye movement when facing the prospect of a potential monetary gain might reflect a conflict between the motivation to approach a reward-related stimulus and the antisaccade instruction of having to gaze away from it. In non-human primate studies, such conflicts between cognitive and motivational task requirements for internally-guided saccades such as memory-guided saccades and their errors have been reported (memory-guided saccades are eye movements towards a remembered location, see also Figure 3-1). For example, in a study by Takikawa et al. (2002), monkeys had to perform memory-guided saccades towards four different directions, only one of them being associated with reward. When examining the trajectories of erroneous saccades, the researchers noticed that they had curved shapes, the saccade initially being directed towards the required, non-rewarded location, but in mid-flight diverted to the rewarded location, and vice versa for some of the

correct saccades. Thus, these results indicate that adolescents are not only hampered for visually-guided prosaccades by the threat of losing money, but also for the preparation of internally-guided antisaccades by the prospect of obtaining rewards.

In contrast to prosaccades and antisaccade direction errors, there was no age-specific modulation of dynamic saccade parameters by incentives for correct antisaccades. This finding was expected based on the higher cognitive control that is necessary for the performance of a correct antisaccade (see also chapter 3.1). The advance of neuroimaging studies in child populations has accumulated evidence indicating that the lower the age and the more fragile the emotional mental health of an individual (i.e. adolescents with mood disturbances vs. healthy adolescents vs. adults), the stronger the activation of subcortical limbic brain areas associated with evaluation of the emotional significance of stimuli such as the nucleus accumbens (NAcc) and amygdala (for review on these neural circuits, see chapter 2.2.1.1) by emotionally challenging stimuli such as threats or rewards - unless attention is captured by cognitively demanding operations, in which case lower age and mood disturbances are associated with increased recruitment of prefrontal cortical areas (Levesque et al., 2004; Monk, McClure et al., 2003) (see chapters 2.2.2 and 2.2.3). These findings have been employed to suggest that recruitment of cognitive control as a major function of the prefrontal cortex (for review see chapter 2.1.2) may normalize function of subcortical brain regions mediating affective states and impulses (e.g. Monk et al., 2008). Similar conclusions can be drawn from clinical and every-day observations with adolescents. For example, on the Stroop color-naming task, phobic individuals commonly show a naming interference effect of threat-related stimuli (i.e. they are slower to name the color in which a word with a threatening emotional content is written) – unless they are tested in close physical or temporal vicinity to their phobic object in which case they show no interference effect presumably due to the recruitment of additional cognitive resources (a process called “strategic override”, for review see Mogg & Bradley, 1998). In addition, many parents and teachers have made the painful observation that adolescents are very well able to reflect on the negative consequences of risky actions such as smoking or unsafe sexual behaviors until they are in midst their peers, where they will commit these very same actions they rated as highly dangerous before (for review and reflection see also Steinberg, 2004, 2005). This phenomenon of note has lead developmental neuroscientists to ask for experimental designs in which adolescent behavioral propensities are probed under “hot” cognitions and under closer approximations of real-life situations, as opposed to asking adolescents on their thoughts about hypothetical risk scenarios.

Finally, in contrast to the findings on the primary saccades after target onset (i.e. correct pro- and antisaccades, and antisaccade direction errors) a more complex picture emerged for dynamics of secondary, corrective saccades. Here, not only adolescents, but also adults showed a significant within-group modulation of dynamic performance parameters by incentives, and this pattern of modulation differed between groups. In terms of latency, adolescents initiated corrective gazes faster on both incentive conditions as compared to the neutral condition, while adults had longer saccade latency for the reward as compared to the punishment and neutral conditions. In terms of peak velocity and amplitude, only adults, but not adolescents showed a modulation by incentives. Specifically,

adults had higher peak velocity and larger saccade amplitude for the reward as compared to the neutral condition, and larger amplitude for the reward as compared to the neutral and punishment conditions.

This pattern of findings for corrective saccades indicates that whereas performance in adults for primary saccades may have reached a ceiling that could not be modulated substantially by context (i.e. incentives) anymore, initiation and regulation of corrective saccades was actually based on information about incentives in this age group. Correction of a direction error depends on two basic sets of mechanisms, one responsible for error detection, and one for initiating remedial actions (Nieuwenhuis, Ridderinkhof, Blom, Band, & Kok, 2001). Neuroimaging, neuropsychological, electrophysiological and non-human primate studies implicate the Anterior Cingulate Cortex (ACC, for review see Bush et al., 2000; Paus, 2001; Rushworth et al., 2004) and for eye movements also the adjacent SEF (Stuphorn et al., 2000) in such an error processing system. Both receive dopaminergic input from the VTA (Gaspar et al., 1992) and thus are able to base error monitoring on information about environmental contingencies (for review on incentive-related modulation of ACC activity, see Rushworth et al., 2004). According to Rushworth et al. (2004, pg. 416) the "ACC's most crucial contribution in the domain of action-outcome associations may be in guiding decisions whether the expected value of a reward means that it is worth acting". The current results of stronger modulation of corrective saccades by incentives in adults as compared to adolescents thus may reflect a progressively more efficient error monitoring system with age that facilitates remedial behavior and maintenance of goal-related actions in situations for which a reward can be obtained. This notion is also supported by the finding that adults corrected their errors significantly earlier than adolescents (mean correction time for adults was 124.87 ± 79.90ms, for adolescents 229.63 ± 139.23ms), and corrected more errors than adolescents although this difference did not reach significance (proportion of antisaccade error corrected by adults: 80.46 ± 24.05%; and adolescents: 71.63 ± 20.16%; $F_{1,60} = 2.47$, $p = 0.121$, n.s).

In sum, as hypothesized, RST task performance was improved by incentives in both age groups, in particular under conditions of high cognitive control (i.e. for correct antisaccades, and in adults for corrective saccades), but deteriorated performance of adolescents under conditions of low cognitive control (i.e. visually-guided eye movements such as prosaccades and antisaccade direction errors). In a previous study using the RST (Jazbec et al., 2006), similar findings were reported, although this study was based on a smaller sample size and used different data extraction procedures. Specifically, Jazbec et al. (2006) reported improved accuracy for the prospect of winning a monetary reward, and decreased accuracy on prosaccades for the threat of monetary loss. In terms of dynamic performance measures, Jazbec et al. (2006) reported similarly to the current study no differences between groups in incentive-related modulation of correct antisaccades, but of antisaccade direction errors. However, in contrast to the present results, no differences were found in incentive-related modulation of correct prosaccades. These findings are also consistent with the one study in human adults (24 males, age 29.3 ± 6.2 years) that examined the effect of monetary incentives on visually-guided saccades, antisaccades, and memory-guided saccades (Duka & Lupp, 1997). Similarly to the current study, Duka and Lupp (1997) reported that monetary reward improved accuracy of antisac-

cades, without affecting dynamic antisaccade parameters. However, in contrast to the current study, Duka and Lupp (1997) did not find an influence of the prospect of monetary reward on accuracy of visually-guided saccades. This disparity in findings might be due to differences between the two studies in the way in which monetary incentives were administered: While in Duka and Lupp (1997) study the monetary incentive was a global “honorarium” at the end of testing for a “particularly good performance”, it was delivered in the current study on a trial-by-trial basis in conjunction with immediate performance outcome notification. Finally, the findings from this study are partly supported by findings from non-human primate studies reporting in line with the data obtained here an influence of incentives on dynamic parameters of eye movements, but in contrast to the current findings for internally-guided saccades. Specifically, in non-human primates, memory-guided saccades have been reported to have shorter latency (Kawagoe et al., 1998; Kobayashi et al., 2002; Lauwereyns, Watanabe et al., 2002; Roesch & Olson, 2003; Takikawa, Kawagoe, Itoh et al., 2002), faster peak velocity (Kawagoe et al., 1998; Kobayashi et al., 2002; Leon & Shadlen, 1999; Roesch & Olson, 2003; Takikawa, Kawagoe, Itoh et al., 2002); and lower rates of error and fixation breaks (Kobayashi et al., 2002; Lauwereyns, Takikawa et al., 2002; Roesch & Olson, 2003; Takikawa, Kawagoe, Itoh et al., 2002) under expectation of (high) reward as compared to no or low reward. This disparity of findings may be due to species-specific differences in neural circuits underlying cognitive control, and/or differences in susceptibility to incentives of neural substrates underlying antisaccade versus memory-guided saccade performance.

7.1.4 Incentive-related modulation of RST performance: Implications for brain maturation

What conclusions can be drawn from these findings of differential developmental modulation of saccadic eye movements of differing cognitive demand by incentives about the maturation of reward-related neural circuits during adolescence and the interaction of cognitive-regulatory and affective brain systems? As reviewed in chapter 3.5, the influence of incentives on saccade performance has been proposed to be mediated by cortical inputs, and/or by the basal ganglia pathway projecting directly or indirectly to the superior colliculus and the saccade generation network in the brainstem. In both of these brain regions, neurons are modulated by incentives before, during or after performance of internally-guided saccadic eye movements. For example, a subpopulation of neurons in the monkey LPFC and DLPFC have been shown to adjust their firing rate in relation to presence or absence of reward on a memory-guided saccade task (Kobayashi et al., 2002; Leon & Shadlen, 1999). Similar results have been obtained for the SEF (Amador, Schlag-Rey, & Schlag, 2000; Stuphorn et al., 2000) and ACC (Niki & Watanabe, 1976, 1979; Sweeney, Takarae, Macmillan, Luna, & Minshew, 2004), however, here incentive-related modulation of neural activity is temporally more closely related to delivery of reward after performance of the operant response, which would comply with the notion of these brain areas being involved in performance monitoring (see above). In a careful study by Roesch and Olson (2003) neurons from several frontal cortical areas (i.e. DLPFC, SEF, SMA, FEF, and in particular in the premotor cortex) showed enhanced responses for expectation of a large versus a

small reward in a memory-guided saccade task. Similarly, in the basal ganglia caudate nucleus (CN) neurons have been shown to exhibit enhanced activity before and after presentation of a cue instructing a specific eye movement during a reward-associated memory-guided saccade task (Lauwereyns, Takikawa et al., 2002; Lauwereyns, Watanabe et al., 2002). According to the authors, anticipatory activity of CN neurons might lead to an enhancement of visual discrimination of the cue by CN projections to the cortex, and/or inhibit the substantia nigra par reticulata (SNPr) in the midbrain which in turn would facilitate saccade generation by the superior colliculus (SC) (Lauwereyns, Takikawa et al., 2002; Sato & Hikosaka, 2002) (for review on the basal ganglia pathway to the brainstem generation network, see Figure 3-3). Indeed, incentive-related modulation of neural activity has also been reported for the SNpr (Sato & Hikosaka, 2002) and SC (Ikeda, Takikawa, & Hikosaka, 2001) neurons, and activity in CN neurons has been shown to correlate positively with saccade peak velocity and saccade latency (Kawagoe et al., 1998). Based on these results, it has been suggested that while the prefrontal cortex changes the cognitive aspects of behavior based on expected reward outcomes, the basal ganglia changes its motor aspects (Kobayashi et al., 2002).

Putting the findings from the non-human primate studies just reviewed in relation to a) developmental cognitive neuroscience models proposing enhanced dopaminergic activity at the level of the Nucleus accumbens (NAcc) in adolescence (Chambers & Potenza, 2003; Chambers et al., 2003), b) reports from fMRI studies showing enhanced activity in the NAcc in response to rewards in adolescents as compared to adults (Ernst et al., 2005; Galvan et al., 2006), and to c) reports from functional and structural MRI showing ongoing functional and structural integration of neural networks orchestrated by the PFC including the ACC up until early adulthood (Davies, Segalowitz, & Gavin, 2004; Giedd, 2004) – i.e. brain regions that have been implicated in goal-directed behavior, executive cognitive control, response conflict resolution between incongruent responses, and error monitoring (for review see Miller & D'Esposito, 2005; Rushworth et al., 2004), the current results may indicate that the prospect of winning money and threat of losing money could have led in adolescents to higher pretarget neural activity in the basal ganglia as compared to adults, facilitating saccade initiation congruent with the motivational, but not the cognitive demand of task performance, whereas the resulting response conflict could not be tempered by regulatory prefrontal control. Such an interpretation is also supported by the study of Duka and Lupp (1997) investigating the effect of monetary incentives and administration of the dopamine agonist levodopa on antisaccade performance in adults: While incentives improved antisaccade performance, administration of levodopa increased antisaccade error rate. The authors tried to reconcile these seemingly contradictory findings by proposing that administration of levodopa might have lead to an increase of dopamine subcortically in the basal ganglia that might have increased responsiveness, while incentives improved cognitive control prefrontally. Similarly, increased antisaccade error rates and latency have been observed after administration of amphetamine in chronic amphetamine abusers (Dursun, Wright, & Reveley, 1999), and finally subcortical hyperdopaminergia and/or prefrontal hypodopaminergia have been implicated in leading to increased antisaccade error rates and antisaccade latencies in patients with schizophrenia (e.g. Fukushima et

al., 2000; Hutton & Ettinger, 2006). Further research, combining the RST with fMRI is needed to further address these hypotheses.

7.1.5 Feedback notification

For the feedback notification period of the RST, it was hypothesized that adolescents would be less sensitive for negative feedback as compared to adults. Findings supported this hypothesis. Specifically, while adolescents did not show a different modulation of pupil dilation by incentive conditions for negative feedback, adults dilated the pupil significantly more when obtaining negative feedback for the reward condition (i.e. notification of not winning money) and on a trend level for the punishment condition (i.e. notification of losing money) as compared to the non-incentive, neutral condition (notification of inaccurate performance without monetary implications). Moreover, adults differed significantly from adolescents in pupil dilation for both incentive conditions, with adults showing greater pupil dilation than adolescents. For absolute pupil diameter, stronger modulation of pupil diameter by incentives was obtained in adults as compared to adolescents, although such a modulation could be observed for adolescents as well.

Reduced influence of negative feedback in adolescents as compared to adults was expected based on the triadic model proposed by Ernst et al. (2006) which suggests that decreased activity of harm-avoidant brain systems such as the amygdala in conjunction with insufficient PFC control may contribute to increased risk-taking behavior during adolescence (see chapter 2.2.2.4). In support for this assumption, Ernst et al. (2005) reported reduced activity in the amygdala after notification of not winning money in a monetary decision-making task in adolescents as compared to adults.

Behaviorally, reduced pupil dilation indexes reduced attentional engagement by feedback notification and/or reduced cognitive processing of feedback in adolescents as compared to adults (Beatty, 1982; Joos et al., 2003; Liversedge & Findlay, 2000; Steinhauer & Hakerem, 1992; Steinhauer et al., 2004). Reports of pupil dilation after amygdala stimulation (Koikegami & Yoshida, 1953) and DLPFC recruitment (Siegle et al., 2003) indeed suggest that this might be due to reduced activity in the amygdala and/or DLPFC in adolescents as compared to adults. However, more research on the RST in combination with neuroimaging methods is necessary to make more definite conclusions about the underlying neural mechanisms mediating this finding.

7.2 Clinical study

For the clinical part of this study, it was hypothesized that 1) diagnostic state would not influence task performance based on reports of little or no difference in saccade performance between adults with MDD and controls (for review see Sweeney et al., 2002), however 2) that adolescents from the control group would differ from adolescents with mood and anxiety disorders in the way they modulate task performance parameters by incentives. Specifically, it was expected that adolescents with MDD would show a weaker modulation of task parameters based on notions of low positive affect and anhedonia in depression, which can be operationalized as decreased effort (motivation) to obtain positive outcomes (i.e. obtain rewards and avoid punishments). In contrast, for patients with an anxiety disorders, it was hypothesized that they would show an attentional bias for negative information and exhibit a strong motivation to avoid negative outcomes (i.e. avoid monetary punishment) based on notions of hypersensitivity to threats in anxiety disorders. Finally, it was hypothesized that 3) controls would differ from both patient groups in the way they respond to outcome notification. Here, it was expected that again based on the notion of decreased positive affect patients with MDD would be less responsive to positive outcomes than controls, indexed by less reactivity of autonomous responses such as (change in) pupil diameter when receiving positive performance feedback. For patients with anxiety, it was expected that based on the notion of hypersensitivity to punishment they would avoid negative information as compared to controls, indexed by shorter fixation duration and/or decreased pupil dilation when receiving negative feedback.

The findings largely support these hypotheses. First, there were no significant main effects of diagnosis on any single task parameter investigated, indicating that the three groups did not differ in their ability to perform internally- and externally-guided eye movements per se. However, groups differed in the way they modulated different saccade parameters by incentives: Specifically, while adolescents from the control group showed a clear improvement of task performance by incentives under high, but less so for low cognitive control, patients with MDD failed to optimize monetary pay-off regardless of saccade type, and patients with anxiety exhibited an attentional bias for the punishment condition. Results will be discussed below in more detail addressing incentive-related modulation of task parameters for each clinical group in relation to performance of the control group. For a more detailed discussion of the performance pattern observed in the adolescent group, the reader is referred to chapter 7.1.

7.2.1 Modulation of RST performance in adolescents with MDD

Whereas adolescents from the control group showed a clear influence of incentives on RST performance, with improvement by incentives for saccades of high cognitive control (i.e. antisaccades, corrective saccades), but interference by incentives for saccades of low cognitive control (i.e. visually-guided prosaccades and antisaccade direction errors), patients with MDD were not able to modulate performance on the RST to maximize financial pay-off.

For example, in terms of global performance measures, patients with MDD did not show an improvement under the prospect of monetary gain (i.e. the reward condition) as compared to the non-incentive, neutral condition for both prosaccade and antisaccade trials, which is at a stark contrast to performance of adult and adolescent controls. In addition, patients with MDD did not modulate global performance in order to avoid a monetary punishment. For example, in contrast to controls, patients with MDD did not perform better on antisaccade trials under the punishment condition, where avoiding the threat-associated stimulus was congruent with the task requirement of moving the eyes away from the target. On prosaccade trials, patients with MDD similarly to controls had worse performance under the punishment condition as compared to the reward condition, but in contrast to controls they also performed worse under the punishment condition as compared to the non-incentive, neutral condition. Finally, patients with MDD corrected on a trend level but with a relevant effect size of 0.43 (for discussion on effect sizes, see chapter 7.3) less antisaccade direction errors that occurred under the punishment condition as compared to the neutral condition, whereas controls and patients with an anxiety disorder showed the opposite pattern of incentive-related modulation of correction of erroneous responses. In sum, the global performance pattern of patients with MDD under incentives supports the hypothesis that patients with MDD did *not put forth effort to obtain reward*, *nor to avoid punishment*. In fact, there seemed to be a deterioration of global task performance in patients with MDD under the threat of monetary punishment.

This pattern of (absent) incentive-related modulation in patients with MDD was expected based on clinical observations, etiological models of MDD and previous behavioral results in adults and adolescents with MDD. For example, as reviewed in chapter 2.2.3.1.2, the research group around Dahl and Forbes (e.g. Forbes et al., 2006; Forbes & Dahl, 2005; Forbes et al., 2007) propose that not only adults but also adolescents with MDD suffer from decreased positive affect, which they suggest is reflected in either decreased motivation to pursue natural or conditioned rewards, and/or diminished subjective experience of enjoying rewards. In adults, several models have been postulated that at their core propose a reduction in positive affect for patients with MDD, such as the “tripartite model” (Clark & Watson, 1991), the reduced social reinforcement-model (Lewinsohn et al., 1985) or the under-active behavioral facilitation system-model in MDD (Depue & Iacono, 1989). In addition, behavioral studies in adults with MDD consistently document decreased responsivity to experimentally presented positive stimuli. For example, adults with depression or dysphoria versus controls have been shown to exhibit less positive expressive behavior in response to pleasant film and drink stimuli (Berenbaum & Oltmanns, 1992) or pleasant pictorial stimuli (Sloan et al., 1997; Sloan et al., 2001), to exhibit reduced heart rate reactivity to amusing short films (Rottenberg et al., 2002), reduced facial EMG reactivity to happy but not sad facial expressions (Sloan et al., 2002), and finally to exhibit a failure in response bias for monetary rewards (Henriques & Davidson, 2000; Henriques et al., 1994; Hughes et al., 1985; Pizzagalli et al., 2005). Indeed, the studies investigating responses to monetary rewards in adult MDD are grossly in line with the results obtained in the current thesis for adolescents with MDD. For example, in the study by Henriques and Davidson (2000) performance of adults with MDD and controls was compared on a verbal recognition task under monetary incentives (reward of 0.10$ for a correct re-

sponse), monetary penalty (loss of 0.10$ for an incorrect response) or a neutral condition (accuracy feedback without monetary implication). Results indicated that while controls showed an approach-related behavior that served to maximize their monetary earnings, patients with MDD did not change their pattern of responding for either the reward condition, and when excluding patients with comorbid anxiety disorders, also for the punishment condition. Similarly, in the study by Pizzagalli et al. (2005) subjects with high scores on the BDI failed to show an increase in facilitatory behavior on a signal-detection task in response to a reinforcing monetary stimulus. In terms of *adolescent* MDD, a recently published behavioral study by Forbes et al. (2007) reported that boys with a depressive disorder fail to choose options with high probability of yielding a high monetary reward on a reward-related decision-making task. However, somewhat surprisingly, to my knowledge no research has investigated reward-related behavior in depressed adolescents with psychophysiological or neuroscience -based methods prior to the data published in this thesis (Jazbec et al., 2005). In the Jazbec et al. (2005) study using the RST, but with less subjects and different data extraction procedures, reduced reactivity in adolescents with MDD to incentives also has been reported, however, in this study results were analyzed selectively for antisaccade direction errors.

Similarly to the results obtained for global performance measures, adolescents with MDD also did not show any significant within-group modulation by incentives for dynamic performance measures such as latency, peak velocity and amplitude. These findings are in line with the results on global task performance and studies outlined above (Henriques & Davidson, 2000; Henriques et al., 1994; Pizzagalli et al., 2005) and extend the results from the eye movement study by Jazbec et al. (2005) and Hardin et al. (2007), both reporting no modulation of latency and peak velocity of antisaccade direction errors by incentives in adolescent patients with MDD. Yet, despite the lack of significant effects, closer examination of the data revealed several consistent trends for a within-group incentive-related modulation of dynamic antisaccade parameters in patients with MDD, all with practically relevant effect sizes of above 0.4. Specifically, patients with MDD differed in their modulation of dynamic performance parameters between the reward and neutral, respectively the punishment condition. Moreover, there were significant group differences between adolescents with MDD and controls for dynamic measures of correct antisaccades, with patients initiating saccades earlier, with faster peak velocity and with larger amplitude as compared to controls under the threat of monetary loss. These results point towards a greater interference of incentives on motor behavior under conditions of high cognitive control in adolescents with MDD as compared to controls or patients with anxiety, with reward possibly improving cognitive control (i.e. similar performance between controls and patients with MDD on the reward condition), and punishment deteriorating cognitive control (differences between groups on the punishment condition). Indeed, adults with MDD commonly have been reported to show state-dependant impairments in several functions underlying executive cognitive control such as working memory, attentional set shifting, and response inhibition (for review see Austin, Mitchell, & Goodwin, 2001; Rogers et al., 2004). For example, Sweeney et al. (1998) reported increased antisaccade errors rates and dysmetric visually-guided saccades in a sample of severely depressed adults with MDD, the latter finding also being found in the adolescent patient group in this study.

Finally, for the outcome notification period of the RST, it was hypothesized that patients with MDD would show less engagement by positive outcomes, as evidenced by shorter fixation duration and/or decreased pupil dilation both of which are measures of attentional engagement and/or cognitive demand (for review see Beatty, 1982; Joos et al., 2003; Steinhauer & Hakerem, 1992; Steinhauer et al., 2004). Yet, in contrast to predictions, there was no significant difference between patients with MDD and controls for positive feedback for any of the parameters measured. However, for negative feedback, patients with MDD fixated notification of a monetary loss significantly longer than did controls or patients with anxiety. Such a finding suggests that patients with MDD devoted more processing resources to notification of negative feedback as compared to the other diagnostic groups. This finding is in line with reports on attentional biases in patients with depression, for example found on the visual dot-probe task, which is a reaction time task analogue to the emotional Stroop task, but with visual instead of verbal stimuli. These studies have consistently reported an attentional bias for subjects with MDD or subclinical depression for negative information that is displayed for longer stimulus durations of about one second (Bradley, Mogg, & Lee, 1997; Gotlib, Krasnoperova, Yue, & Joormann, 2004; Mogg, Bradley, & Williams, 1995). In terms of eye movement studies, Eizenman, Yu et al. (2003) and Caseras, Garner, Bradley, and Mogg (2007) found that adults with depression or dysphoria fixate pictures depicting negative scenes longer as compared to neutral pictures respectively as compared to controls. As pointed out by Caseras et al. (2007), a bias in the maintenance of attention on negative information may be an important factor sustaining dysphoric mood, and could be caused by difficulty in disengaging attention from the spatial location of negative cues, or enhanced elaborative processing of negative material. The current data indicates that such a bias for processing negative information is already evident in eye movement parameters of adolescents with MDD.

In sum, adolescents with MDD in contrast to adolescent controls showed no improvement of global performance on the RST under incentives, and exhibited a sound tendency for incentives to influence dynamic parameters of eye movements of high cognitive demand. Moreover, patients with MDD exhibited an attentional bias for negative information, as indexed by longer fixation duration for negative outcomes. These results are in line with models and findings on adult and adolescent MDD suggesting not only a decrease in reward-seeking behaviors and positive affect (e.g. Depue & Iacono, 1989; Forbes et al., 2006; Forbes & Dahl, 2005; Forbes et al., 2007), but also an increase in negative affect (Clark & Watson, 1991; Joiner et al., 1996; Joiner & Lonigan, 2000; Lonigan, Hooe, David, & Kistner, 1999; Lonigan, Phillips, & Hooe, 2003; Lonigan et al., 2004; Watson et al., 1995). For example, Lonigan et al. (2004) have proposed that increased negative affect in conjunction with low executive control may be a risk factor for developing an internalizing disorder such as an anxiety or depressive disorder in youth (see also chapter 2.2.3.1.3).

What conclusions can be drawn from these findings about the underlying neural mechanisms that may mark vulnerability for suffering from depression in adulthood? In adult MDD, prominent neuroscience models based on a variety of research methods suggest hypofunction of cognitive-executive brain systems such as the DLPFC, and hyperfunction of affective brain systems such as the orbitofrontal and ventromedial PFC and the amygdala, with an important role of the ACC in reciprocally

balancing activity in these two systems (R. J. Davidson et al., 2002; Drevets, 2000, 2001; Mayberg, 1997; Phillips, Drevets, Rauch, & Lane, 2003b) (see also chapter 2.2.1 and Figure 2-11). In addition, several authors have proposed dysfunction of the mesocorticolimbic dopaminergic system in depression (Depue & Collins, 1999; Drevets, 2001; Nestler & Carlezon, 2006). Similarly, for adolescent internalizing disorders, models such as the triadic model (Ernst et al., 2006) or the social information processing network model (Nelson et al., 2005) suggest reduced regulatory prefrontal control over affective neural systems, with some additionally proposing either enhanced activity of the amygdala (Ernst et al., 2006) and/or dysfunction of the mesocorticolimbic reward system (Ernst et al., 2006; Forbes & Dahl, 2005).

Recently, several functional imaging studies have been published that have investigated brain activation in adolescents with MDD in response to affective stimuli (Forbes et al., 2007; Killgore & Yurgelun-Todd, 2006; Monk et al., 2008; Roberson-Nay et al., 2006; Thomas et al., 2001). For example, Forbes et al. (2007) reported diminished activity in the ACC, ventral OFC, and striatum (bilateral caudate nucleus) and increased activity in the dorsal OFC in adolescents with MDD as compared to controls during anticipation for responding to reward. Similarly, in a very recent study by Monk et al. (2008), adolescents at familial risk for developing MDD activated the NAcc less when viewing happy faces, and the amygdala more when viewing fearful faces as compared to controls. However, these differences in brain activation were only evident when attention was unconstrained (i.e. under low cognitive control), but not when attention was captured by a cognitive demand (rating the nose width of the face seen), which was associated with higher recruitment of the medial PFC in at-risk adolescents as compared to controls. Killgore and Yurgelun-Todd (2006) reported enhanced neural activity in the ventromedial PFC including the medial OFC and rostral ACC in dysphoric adolescents while viewing faces with fear expressions. Finally, Roberson-Nay et al. (2006) found enhanced amygdala activation in adolescents with MDD during incidental encoding of faces. In light of these findings, the current results of absent improvement of RST task performance by incentives in adolescents with MDD as compared to controls may indicate reduced activation of the mesocorticolimbic brain system by rewards, while the deterioration of RST performance under threat of monetary loss and attentional engagement by notification of monetary loss may indicate enhanced activity of the amygdala by punishments. Finally, the trends for an interference of incentives on dynamic performance measures under conditions of high cognitive control but not low cognitive control in adolescents with MDD are difficult to put in relation to the existing data. Since dynamic performance measures of internally-guided saccades have been proposed to be mediated through its basal-ganglia-superior-colliculus pathway (Kawagoe et al., 1998; Lauwereyns, Takikawa et al., 2002; Takikawa, Kawagoe, & Hikosaka, 2002) these findings may indicate a weaker top-down modulatory influence on basal-ganglia pathways in adolescents with MDD as compared to controls. However, as also pointed out in chapter 7.3, further studies in greater patient samples and combining the RST with neuroimaging methods are necessary to replicate these findings and to allow sound conclusions about the neural pathways and systems that may exhibit dysfunction in adolescent MDD during performance of the RST.

7.2.2 Modulation of RST performance in adolescents with an Anxiety Disorder

Patients with an anxiety disorder were expected to exhibit an attentional bias for negative information and a strong motivation to avoid negative outcomes (i.e. avoiding monetary punishment). Specifically, it was hypothesized that adolescents with anxiety will perform better on punishment trials (i.e. better accuracy, earlier saccade latencies) as compared to neutral trials and as compared to controls. For the outcome notification period, it was hypothesized that anxious patients will avoid negative information more than controls, as indexed by shorter fixation duration and smaller pupil dilation for notification of negative feedback.

Findings partly support these hypotheses. First, patients with anxiety initiated prosaccades on a trend level faster than did controls on punishment trials ($p = 0.058$, effect size = 0.52), and corrected more antisaccade direction errors than controls on the punishment condition ($p = 0.006$, effect size = 0.73). These findings are in line with several cognitive models on anxiety proposing preconscious attentional biases in anxious individuals towards threats (e.g. Eysenck, 1992; Mathews, May, Mogg, & Eysenck, 1990; J. M. G. Williams, Watts, MacLeod, & Mathews, 1997) and in line with empirical evidence assessing attentional biases in adult and adolescent patients with an anxiety disorder (for review in adults, see Bishop, 2007; for review in youth, see Pine, 2007). For example, on the modified Stroop color-naming task, where subjects have to name the color in which words with emotional contents are written, patients with anxiety name words with threatening contents later than controls, which commonly is interpreted in terms of anxious individuals‘ attention being captured by the threat content of the word (for review see Mogg & Bradley, 1998). On probe detection tasks, where reaction time to a visual probe is used as an index of spatial attention, patients with anxiety respond faster to a probe if it replaces a threatening word or if it replaces a picture depicting a threatening scene, as compared to a word or picture with a neutral content, and as compared to controls, which is consistent with an attentional bias favoring threats (e.g. MacLeod et al., 1986). Finally, on dot-probe tasks assessing orientation of eye movements, adults with anxiety tend to orient their gaze faster at pictures depicting angry or fearful faces relative to happy or neutral faces and as compared to non-anxious individuals (Mogg, Garner, & Bradley, 2007; e.g. Mogg et al., 2000; Mogg, Philippot, & Bradley, 2004). Thus, the current finding of shorter latency for prosaccades under the punishment condition and a higher rate of corrective gazes under the punishment condition indicates a selective bias for processing threat-related stimuli in adolescents with anxiety. A selective orientation bias towards threatening information is further supported by the finding that patients with anxiety disorders did not differ from controls in latency of correct antisaccades on punishment trials, where the gaze had to be directed away from the threatening cue/stimulus.

In addition, patients with anxiety differed from controls on neutral trials for peak velocity of correct antisaccades, and on a trend level for correct prosaccades, where controls but not patients slowed down on neutral trials. Since peak velocity may be used as an indicator of alertness and arousal (for review see Khan et al., 2000), this finding indicates that patients with anxiety were highly activated by the RST, independent of financial pay-off. Additional support for the notion of an in-

creased level of arousal in patients with anxiety might be the absent within-group modulation of task parameters by incentives: With exception for percent correct prosaccades, where patients with anxiety similarly to controls performed significantly better on the reward as compared to the punishment condition, no other parameter of any saccade type was modulated differently between the three incentive conditions for patients with anxiety. An increased level of arousal in anxiety has also been postulated by cognitive-affective models on anxiety. For example, the "tripartite model" by Clark and Watson (1991) proposes that anxiety in contrast to depression is characterized by physiological hyperarousal and Eysenck (1987) has proposed that individuals with high trait anxiety are not only prone to attend preferentially to threat stimuli (which he termed specific hypervigilance), but to exhibit a general hypervigilance also to task-irrelevant stimuli, in order to detect a salient stimulus quicker.

Attentional bias for threats might depend on the stage of information processing. For example, Mogg et al. (1992) and Mathews (1990; 1993) have proposed that individuals with high anxiety exhibit a "vigilance-avoidance" pattern of bias, with initially directing attention to threats, but subsequently diverting attention away from threats in order to reduce discomfort. Such a vigilance-avoidance pattern of attention is supported by a study by Hamm, Cuthbert, Globisch, and Vaitl (1997), where subjects with specific phobia had shorter viewing times of pictures of their own phobic objects. However, results from the current study do only support a vigilance, but not an avoidance pattern of attention bias in adolescents with an anxiety disorder. Specifically, adolescents with anxiety differed from controls only in parameters investigated during the performance period of the RST, but not in parameters investigated during the outcome notification period.

In terms of underlying neural substrates, attentional bias for threat in anxiety commonly has been implicated to reflect perturbation in amygdale-ventrolateral PFC circuitry. As reviewed in chapter 2.2.3.1.3, the amygdala is proposed to be hyperactive in anxiety, while the PFC is proposed to exert insufficient regulatory control to deploy attention in a goal-related manner despite threat-interference (for review in adults see Bishop, 2007; for review in youth see Pine, 2007). In adolescents, only one neuroimaging study to date has directly investigated orienting to threats in youth with anxiety (Monk et al., 2006). In this study, adolescents with GAD performing a threat-dot-probe task exhibited enhanced activity in the ventrolateral PFC as compared to controls, and level of activation was negatively correlated with anxiety levels. In addition, three brain imaging studies have shown increased amygdala activation in youth with an anxiety disorder while passively viewing fear faces (Killgore & Yurgelun-Todd, 2005; McClure et al., 2007; Thomas et al., 2001). In the McClure et al. (2007) study, when engaging attention in a non-emotional rating (how wide is the nose?), activity in the amygdala normalized to control level, suggesting that recruitment of cognitive control processes might moderate differences in amygdala reactivity between diagnostic groups. In light of this brief review, the current results might indicate enhanced amygdala activity under threat of monetary loss in the RST in anxious adolescents as compared to controls in particular for conditions of low cognitive control such as for prosaccade trials, while the overall high level of arousal observed for anxious patients and the cognitively demanding nature of the task in particular for antisaccade trials might have prevented to detect more strong differences between diagnostic groups.

7.3 Limitations and Implications for Future Work

These results need to be considered in the light of some limitations. First, the sample sizes in the clinical study were small, particularly with respect to patients with MDD. However, sample size was sufficiently large to detect differences between groups. In addition, effect sizes - a measure on the strength of an effect independent of sample size - were at levels that can be considered practically relevant. The mean effect size for all independent-sample t-tests reported in this thesis following up significant effects or trends on age-related differences in the Analysis of Variance was 0.86 (range: 0.40-1.45, with the very high effect size of 1.45 being observed for latency of corrective saccades), and those on diagnosis-related differences 0.59 (range: 0.43-0.81). The mean effect size for all dependant-sample t-tests investigating within-group differences in the Analysis of Variance was for adults 0.76 (range: 0.35-1.16), for adolescents 0.51 (range: 0.33–0.94), for patients with MDD 0.59 (range: 0.43–0.84), and for patients with an anxiety disorder 0.49 (range: 0.39–0.64). For comparison, the effect size of the significant improvement in proportion of correct antisaccades under incentives reported by Duka and Lupp (1997) in adults was 0.39 as calculated based on their reports on pre- and post means and standard deviations. In the study by Henriques and Davidson (2000) who compared responses of adults with MDD and controls on a verbal memory task under monetary reward, monetary punishment and non-incentive trials, effect sizes of significant within-group differences in modulation of responses by incentive conditions was of 0.30 for the comparison between the reward – neutral condition, and 0.11 for the comparison between the punishment and neutral condition. Nevertheless, although there was sufficient power to detect meaningful effects and interactions, replication in a larger patient sample might reveal additional results.

Second, both clinical groups were heterogeneous in terms of their specific diagnoses. For example, subjects in the anxiety groups suffered from different types of anxiety disorders, and in addition, four subjects in the anxiety group and two subjects in the MDD group suffered from mild ADHD. Analysis of Variance repeated after exclusion of those patients with ADHD (results not reported) did not change the conclusions of this study. Nevertheless, it is difficult to clearly evaluate the potential impact of such comorbidity on the performance of the RST. In addition, for the MDD group adolescents with MDD and comorbid anxiety disorders were combined with adolescents with only MDD. Although the primary diagnosis in these adolescents was MDD, the inclusion of subjects with comorbid anxiety may have diminished potential differences between the anxiety only and MDD groups. Indeed, Analysis of Variance performed after excluding the four subjects with comorbid diagnoses generated identical conclusions, however, significance level of the diagnosis-by-reward(-by-type) interactions observed for dynamic performance measures of correct responses reached higher levels of significance (compare results in Table 9-15 with those in Table 9-16).

Third, an important open question that is not addressed by the current data is whether the observed differences in reward-related behavior in the patient groups are state or trait-related. This question is important in order to evaluate the utility of reward sensitivity and reward-related behavior in adolescents with MDD and anxiety disorders as a risk marker or endophenotype for the development

and/or maintenance of affective disorders later in life. As recently reviewed by Hasler et al. (2004), one of the main challenges in biological psychiatry in the next future will be to improve the phenotypic definition of depression so that a better understanding of the genetic and neurobiological underpinnings of this debilitating disease can be achieved and better and earlier intervention strategies designed. To evaluate the state versus trait character of the present results, it would be useful to test a group of patients with current and remitted symptoms. Similarly, it would be interesting to test the RST under medication with antidepressants.

Fourth, it is possible that motivation to do well on the task was different in patients as compared to healthy subjects because of their seeking treatment. However, it was made clear to these participants that they did not have to complete this task to be included in the subsequent treatment study (investigating the effect of medication with fluoxetine versus placebo). In addition, seeking treatment was initiated by the parents rather than by the adolescents. These circumstances mitigate the possibility of different sources of motivation to do the task between patients and healthy volunteers.

Fifth, interpretation of the present findings should be moderated by some methodological limitations. First, the eye-tracking device had a sampling rate of about 60Hz. Thus, measurement error was ± 8 milliseconds, and may have prevented from detecting differences between groups or conditions. As comparison, the studies investigating the development of different types of saccadic eye movements in children and adolescents have been using devices with sampling rates of 1000Hz (Fischer, Biscaldi et al., 1997), 500Hz (Munoz et al., 1998) or 250 Hz (Kramer et al., 2005), although some researchers also have been using devices with sampling rates similar to the one used in this study (e.g. Fukushima et al., 2000; Karatekin, 2004). Thus, although a rate of 60Hz is sufficient to detect differences in RST accuracy, replication of the study with a device with higher sampling rate would provide better information on the dynamic performance measures of the RST. Second, the nature of the RST was quite complex, targeting several cognitive abilities such as inhibitory control, attentional set shifting, working memory, and processes of associative learning. From the results obtained, it can be concluded that incentives interfere with some of these processes more strongly in youth and adolescents mood and anxiety disorders as compared to adulthood and psychological well-being. However, which of these cognitive functions specifically is disrupted by incentives remains to be investigated. It may be that patients with MDD showed less modulation by incentives because they were not able to differentiate between the significance of specific cues, to associate the significance of a cue with a behavioral action or outcome, or if they were not able to switch between different conditions as fast as were healthy adolescents. In the future, it could be helpful to simplify the RST, for example be looking at blocks of antisaccade and prosaccade trials, and blocks of trials with incentives only, punishments only, and neutral trials only instead of the randomized nature of trial presentation used in the current version. On the other hand, results obtained by Hardin et al. (2007) suggest that it may be exactly the complex nature of the RST that produces the differences observed between diagnostic states, possibly through its higher working memory load or its demand for attentional set shifting. With a modified version of the RST only presenting antisaccade trials under monetary rewards,

punishments and no incentives, Hardin et al. (2007) found differences between groups only for accuracy, but not dynamic performance measures. Finally, monetary rewards and incentives were the same monetary amounts. However, according to prospect theory (Kahneman & Tversky, 1979), the impact of a loss is proposed to exceed the impact of a gain of equal magnitude. If so, larger gains than losses should be used in future studies so as to compensate for the asymmetry in emotional responses. In addition, it might be helpful to include a truly neutral condition, i.e. a condition in which there would be no monetary implications and no feedback on performance accuracy.

Finally, although specific saccadic eye movement parameters have been mapped onto specific neural circuits based on extensive research in non-human primates and humans, sound conclusions about differences in activity of neural circuits underlying reward-related information processing in healthy adolescents versus adults and versus adolescents with either MDD or anxiety can not be drawn, calling for replication of the RST in a neuroimaging environment.

IV. CONCLUSION

Adolescence is increasingly recognized by neuroscientists as a model for understanding the development of affect and its regulation in humans, being a period of heightened emotional turmoil, or "storm and stress". While most adolescents navigate through adolescence without great difficulty, or even experience a period of great strive and passion to achieve adaptive goals, for some it marks the beginning of a life-long battle with affective disturbances. From this background, in an attempt to better understand affect (dys-)regulation during adolescence, this thesis compared cognitive control under incentives in adults, healthy adolescents and adolescents with a major depressive or anxiety disorder. From a developmental perspective, results indicate that incentives influence behavior in adolescence in particular under conditions of decreased cognitive control, whereas from a clinical perspective, results indicate that biases in emotion-attention interactions and perturbation of motivated behaviors reported for adults with depression or an anxiety disorder can already be observed in adolescents afflicted by these disorders.

On a neuroscience-based level, these findings highlight the importance of considering the aspect of interaction between affect and cognition when interested in the pathophysiology of mood and anxiety disorders, and moreover the eligibility of reward-related information processing to probe such interactions. In order to refine the understanding of the neural mechanisms underlying the observed findings, the RST needs to be replicated in conjunction with functional neuroimaging methods. In addition, to answer the question whether the observed biases in emotion-attention and perturbation of motivated behaviors in patients precede the manifestation of symptoms and thus constitute vulnerability factors, or contribute to symptom expressions, the RST would need to be replicated in greater patient samples, spanning a greater age range from early childhood to late adolescence and under tight control of a subject's pubertal status.

Keeping in mind the pitfalls of inconsiderately generalizing findings obtained in a laboratory setting, there nevertheless can be drawn some conclusions from the results of this thesis for every-day living with adolescents and treatment of adolescents with mood and anxiety disorders. On one hand, the results obtained from the clinical study certainly support the calling for an earlier identification and treatment of adolescents suffering from an affective disorder, and moreover support the use of strategies aimed to increase emotion regulation skills in this patient population. Such an earlier identification and treatment of affected youth is not only important in light of the subjective distress associated with suffering from a depressive or anxiety disorder, but also in light of the great, yet transitory, plasticity in brain systems underlying regulatory cognitive control and their integration with affective systems during this age span, as well as in light of the negative implications a dysfunction at this age may have for later psychosocial functioning. In terms of "normative" adolescence, the notion of increased reward sensitivity under low cognitive control asks for caution with use of only cognition or insight-based prevention strategies for drug abuse, safer sex methods or careful driving. There indeed seems to be an

innate inclination of adolescents to explore their borders and respond to temptations offered in the outside world. This has lead some developmental neuroscientists to ask for policies that are oriented towards avoidance of harms coming from risky decisions in addition to educational interventions designed to increase adolescent's knowledge on risky behaviors (e.g. Pechmann et al., 2005; Steinberg, 2004). For example, according to Steinberg (2004, pg. 57) "strategies such as raising the price of cigarettes, more vigilantly enforcing laws governing the sale of alcohol, expanding access to mental health and contraceptive services, and raising the driving age would likely be more effective in limiting adolescent smoking, substance abuse, suicide, pregnancy, and automobile fatalities than strategies aimed at making adolescents wiser, less impulsive, or less short-sighted." On the other hand, simply restricting the world of adolescents will not make their curiosity and seeking of "new territories" and borders disappear. Thus, as important may be to offer adolescents more safe spaces in which they have a right to explore their borders and to be imprudent, and to disclose aims for which to invest their tremendous energies. At the least, the now available knowledge of the vast transformation occurring in an adolescent brain and its functional implications as also evidenced in the current thesis, in conjunction with the physical and social challenges faced by this age group may help adults to better understand adolescent problems and inner turmoil.

V. BIBLIOGRAPHY

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VI. APPENDICES

8. Appendix I: Debriefing Questionnaire

Debriefing Saccade Task

Subject Number	Subject Initials	Date (mm - dd - yy)
☐☐☐☐	☐☐☐	☐☐-☐☐-☐☐

Please answer the questions below using the following 1- 4 scale:

1 not at all 2 a little 3 very 4 extremely

Were you able to distinguish between gray and white instruction cues?	1	2	3	4
How difficult was the task for you?	1	2	3	4
How much did you enjoy doing the task?	1	2	3	4
How excited did you get when you won money?	1	2	3	4
How nervous were you during the task?	1	2	3	4
How bored were you during the task?	1	2	3	4
Did you want to play longer?	1	2	3	4
Did you get upset when you lost $1?	1	2	3	4
Did you get upset when you received negative feedback?	1	2	3	4
Did you try to guess where the star would be?	1	2	3	4
Did the computer make mistakes?	1	2	3	4
Was the task too slow for you?	1	2	3	4
Was the task too fast for you?	1	2	3	4
Did you have trouble looking at the opposite side of the star?	1	2	3	4
How hard was it for you to stay focused on the task?	1	2	3	4
Would you like to do the task again?	1	2	3	4
How tired did you get during the task?	1	2	3	4
How angry did the task make you feel?	1	2	3	4
How sad did the task make you feel?	1	2	3	4
How frustrated did the task make you feel?	1	2	3	4
Did you have trouble sitting still?	1	2	3	4
Do you think the game was rigged ("fixed" by the experimenters)	1	2	3	4
Did your eyes hurt?	1	2	3	4
Did the computer say you were wrong when you were right?	1	2	3	4
Did the computer say you were right when you were wrong?	1	2	3	4
Did you care about the meaning of the sign in the middle of the screen (whether it was a plus, a minus, or a circle)?	1	2	3	4
Were you excited when the central sign was a plus?	1	2	3	4
How much money did you make after? run1_____ run2_____ run3_____				
How rewarding is money to you?	1	2	3	4

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Figure 8-1: Exemplar of Antisaccade Debriefing Questionnaire administered after completion of the task.

9. Appendix II: Tables

9.1 Data selection

Table 9-1: Saccadic responses after target onset (in %; mean, std, N) per subject group (adults, adolescents, adolescents with anxiety disorders, adolescents with MDD). Saccadic responses are listed by the latency of their onset after target presentation (anticipatory = 0-79ms, express = 80-134ms, regular = 135-700ms, true = 80-700ms, and late responses = > 700ms), by instruction type (antisaccades AS, prosaccades PS), and by accuracy (correct responses, direction errors, corrective saccades).

			Adults			Adolescents			Anxious Patients			MDD Patients		
Population		**Proportion of Responses**	mean	std	N	mean	std	N	mean	std	N	mean	std	N
all trials		% responses recorded	98.43	2.05	30	97.27	2.98	32	98.20	1.57	16	97.64	2.28	12
all responses recorded		% anticipatory	1.30	1.74	30	1.48	1.62	32	2.30	2.51	16	1.82	2.28	12
		% express	9.69	12.05	30	8.79	10.48	32	12.67	9.99	16	14.46	20.32	12
		% regular	88.51	12.49	30	88.68	10.76	32	83.75	10.89	16	82.85	21.04	12
		% true	98.20	2.08	30	97.47	2.03	32	96.42	3.85	16	97.31	3.53	12
		% late	0.51	0.99	30	1.05	1.34	32	1.27	1.86	16	0.87	1.76	12
all true responses	AS	% all responses	50.48	1.34	30	48.47	3.65	32	49.82	1.80	16	50.65	1.04	12
		% correct	77.69	13.84	30	63.80	18.81	32	62.60	18.88	16	59.18	23.01	12
		% direction errors	22.31	13.84	30	36.20	18.81	32	37.40	18.88	16	40.82	23.01	12
		% corrected	80.46	24.05	30	71.63	20.16	32	83.22	11.18	16	82.80	17.70	12
	PS	% all responses	49.52	1.34	30	51.53	3.65	32	50.18	1.80	16	49.35	1.04	12
		% correct	97.54	2.81	30	95.39	6.19	32	97.34	2.39	16	95.97	3.58	12
		% direction errors	2.46	2.81	30	4.61	6.19	32	2.66	2.39	16	4.03	3.58	12
		% corrected	41.03	42.29	19	52.81	40.26	27	38.61	35.09	14	74.40	35.31	10

Table 9-2: Fixations after feedback onset (in %; mean, std, N) per subject group (adults, adolescents, adolescents with anxiety disorders, adolescents with MDD).

		Adults			Adolescents			Anxious Patients			MDD Patients		
Population	**Proportion of Responses**	mean	std	N	mean	mean	std	N	mean	mean	std	N	mean
all trials	% fixations recorded	92.09	7.24	30	89.58	8.24	32	88.92	10.86	16	89.96	6.25	12
all fixations recorded	% fixations directed at feedback	91.87	8.24	30	94.22	6.26	32	94.96	3.94	16	92.69	5.82	12
All fixations directed at feedback	% positive feedback	83.80	7.72	30	73.04	11.00	32	70.52	12.24	16	74.94	15.36	12
	% negative feedback	16.20	7.72	30	26.96	11.00	32	29.48	12.24	16	25.06	15.36	12

9.2 Descriptives

Table 9-3: Descriptives (mean, std, N) of saccadic responses analyzed during the performance period of the RST per subject group (adults, control adolescents, adolescents with anxiety disorders, adolescents with MDD).

Dependant Variable per Saccade Type and Incentive Condition			Adults			Adolescents			Anxious Patients			MDD Patients		
			mean	std	N	mean	std	N	mean	std	N	mean	std	N
correct prosaccades	Frequency (%)	punishment	31.54	3.03	30	30.97	3.17	32	31.29	1.89	16	30.23	3.65	12
		reward	33.69	1.95	30	32.91	2.10	32	33.65	2.38	16	32.91	1.87	12
		neutral	32.31	1.79	30	31.51	3.22	32	32.39	1.56	16	32.82	1.77	12
	Latency (ms)	punishment	181.18	22.45	30	192.06	30.91	32	178.16	22.32	16	184.12	42.78	12
		reward	180.24	23.14	30	186.16	26.71	32	174.89	26.12	16	176.46	28.30	12
		neutral	181.09	26.22	30	188.20	33.43	32	179.67	24.52	16	184.38	41.89	12
	Peak Velocity (°vis ang/s)	punishment	89.84	10.43	30	92.94	13.26	32	93.14	11.77	16	90.63	7.91	12
		reward	92.64	12.18	30	91.16	10.22	32	93.79	15.25	16	91.05	5.45	12
		neutral	90.67	13.23	30	88.62	11.03	32	94.46	14.97	16	89.77	6.53	12
	Saccade Duration (ms)	punishment	105.80	12.09	30	104.66	8.01	32	106.23	10.63	16	110.67	9.94	12
		reward	106.21	8.61	30	104.79	8.06	32	105.72	9.30	16	109.43	11.62	12
		neutral	106.19	10.37	30	105.93	7.06	32	107.33	9.06	16	110.01	14.81	12
	Saccade Amplitude (° vis angle)	punishment	4.88	0.42	30	4.94	0.47	32	5.12	0.51	16	5.30	0.68	12
		reward	4.97	0.35	30	4.99	0.39	32	5.14	0.41	16	5.28	0.56	12
		neutral	4.85	0.45	30	4.86	0.39	32	5.11	0.43	16	5.13	0.56	12
correct antisaccades	Frequency (%)	punishment	27.33	5.10	30	23.15	8.11	32	21.30	6.08	16	19.91	9.58	12
		reward	26.83	5.22	30	22.25	5.32	32	21.28	6.29	16	20.56	7.39	12
		neutral	23.54	5.54	30	18.41	7.91	32	20.02	8.92	16	18.71	7.50	12
	Latency (ms)	punishment	260.94	27.63	30	293.67	51.89	32	282.95	41.08	16	247.87	88.37	12
		reward	258.31	28.53	30	284.96	39.54	32	277.78	48.71	16	276.26	53.28	12
		neutral	263.30	30.32	30	293.94	49.67	32	291.76	43.35	16	313.25	93.68	12
	Peak Velocity (°vis ang/s)	punishment	95.04	16.54	30	105.19	31.57	32	108.83	31.10	16	135.66	93.53	12
		reward	96.57	18.11	30	107.64	23.40	32	112.25	25.84	16	101.74	12.14	12
		neutral	94.03	19.77	30	102.40	23.99	32	114.68	23.72	16	113.15	24.97	12
	Saccade Duration (ms)	punishment	119.11	15.17	30	117.07	16.79	32	124.86	26.33	16	125.27	56.28	12
		reward	120.23	19.01	30	121.34	19.53	32	118.22	24.39	16	119.59	17.29	12
		neutral	120.58	16.61	30	118.66	23.32	32	111.59	13.49	16	117.09	11.89	12
	Saccade Amplitude (° vis angle)	punishment	5.71	1.03	30	5.92	1.42	32	6.61	1.56	16	7.03	2.45	12
		reward	5.87	1.16	30	6.16	1.70	32	6.50	1.71	16	6.14	0.73	12
		neutral	5.61	0.83	30	6.12	1.98	32	6.41	1.32	16	6.89	1.64	12
antisaccade direction errors	Frequency (%)	punishment	6.20	4.92	30	10.67	7.64	32	12.23	6.19	16	13.14	9.03	12
		reward	6.38	5.28	30	11.05	5.62	32	11.83	6.04	16	13.45	8.16	12
		neutral	9.73	5.50	30	14.48	7.77	32	13.34	8.69	16	14.23	6.81	12
	Latency (ms)	punishment	187.47	40.80	28	186.60	37.43	31	184.22	40.89	16	178.65	33.83	12
		reward	182.74	42.70	25	206.79	59.22	32	189.08	34.48	16	175.26	30.47	12
		neutral	181.00	31.12	29	183.73	36.58	32	173.10	26.50	16	176.87	31.33	12
	Peak Velocity (°vis ang/s)	punishment	81.75	13.03	28	86.33	16.01	31	90.55	18.96	16	86.02	11.02	12
		reward	91.45	47.78	25	104.37	48.60	32	86.52	12.22	16	88.50	12.62	12
		neutral	84.89	29.76	29	82.49	10.46	32	86.63	17.80	16	86.75	12.78	12
	Saccade Duration (ms)	punishment	107.27	8.68	28	104.66	14.59	31	106.12	16.55	16	109.17	8.77	12
		reward	107.29	21.14	25	105.80	17.93	32	107.35	8.33	16	116.27	14.28	12
		neutral	106.65	7.93	29	107.11	11.80	32	103.87	13.91	16	117.74	30.79	12
	Saccade Amplitude (° vis angle)	punishment	4.51	0.54	28	4.60	0.75	31	4.65	0.62	16	4.87	0.49	12
		reward	4.55	0.64	25	5.11	1.99	32	4.74	0.59	16	5.41	1.24	12
		neutral	4.52	0.81	29	4.66	0.51	32	4.56	0.58	16	5.02	0.85	12
corrective saccades	Frequency (%)	punishment	82.90	28.56	28	74.48	24.53	31	88.57	12.38	16	78.53	22.24	12
		reward	85.96	20.17	25	73.30	28.16	32	84.12	18.73	16	82.55	18.62	12
		neutral	79.30	28.48	29	70.17	27.18	32	75.10	27.62	16	86.04	19.03	12
	Latency (ms)	punishment	111.77	67.13	26	209.39	150.95	30	236.54	177.70	16	269.01	140.72	12
		reward	154.10	107.35	25	198.65	112.27	30	158.62	120.49	16	190.74	110.74	12
		neutral	108.75	64.92	28	280.85	154.47	31	204.21	113.93	15	211.92	164.81	12
	Peak Velocity (°vis ang/s)	punishment	172.61	66.51	26	157.98	23.39	30	195.98	106.54	16	158.35	26.58	12
		reward	175.37	44.93	25	165.78	45.23	30	173.85	63.91	16	166.25	25.47	12
		neutral	153.91	29.72	28	151.01	32.43	31	170.86	55.11	15	165.32	23.63	12
	Saccade Duration (ms)	punishment	117.94	24.16	26	116.54	26.19	30	115.33	29.44	16	120.88	16.49	12
		reward	128.18	36.12	25	119.57	38.54	30	108.33	17.11	16	123.75	27.72	12
		neutral	141.32	108.86	28	131.34	49.44	31	131.29	65.31	15	115.80	17.05	12
	Saccade Amplitude (° vis angle)	punishment	9.38	1.75	26	9.26	1.46	30	9.40	1.49	16	9.77	1.87	12
		reward	10.86	2.18	25	9.52	2.04	30	8.96	2.07	16	10.18	1.22	12
		neutral	10.66	7.92	28	9.30	1.65	31	10.83	4.18	15	9.81	1.54	12

Table 9-4: Descriptives (mean, std, N) of fixation parameters analyzed during the feedback notification period of the RST per subject group (adults, control adolescents, adolescents with anxiety disorders, adolescents with MDD).

Dependant Variable per Feedback Type and Incentive Condition			Adults			Adolescents			Anxious Patients			MDD Patients		
			mean	std	N	mean	std	N	mean	std	N	mean	std	N
Fixation Duration (s)	Positive Feedback	punishment	0.52	0.09	30	0.52	0.10	32	0.56	0.10	16	0.57	0.11	12
		reward	0.54	0.09	30	0.54	0.09	32	0.54	0.07	16	0.55	0.09	12
		neutral	0.53	0.09	30	0.54	0.11	32	0.51	0.11	16	0.56	0.12	12
	Negative Feedback	punishment	0.51	0.16	28	0.51	0.16	32	0.48	0.14	16	0.63	0.22	12
		reward	0.45	0.18	28	0.49	0.15	32	0.50	0.17	16	0.50	0.18	12
		neutral	0.47	0.23	30	0.49	0.14	32	0.47	0.10	16	0.49	0.17	12
	Feedback Combined	punishment	0.52	0.08	30	0.52	0.10	32	0.53	0.08	16	0.57	0.12	12
		reward	0.52	0.10	30	0.52	0.09	32	0.51	0.05	16	0.54	0.10	12
		neutral	0.51	0.09	30	0.53	0.10	32	0.50	0.09	16	0.54	0.12	12
Pupil Diameter (mm)	Positive Feedback	punishment	5.55	1.19	30	7.26	1.56	32	6.70	0.90	16	6.24	0.99	12
		reward	5.56	1.16	30	7.28	1.55	32	6.70	0.86	16	6.27	0.98	12
		neutral	5.47	1.24	30	7.22	1.54	32	6.62	0.88	16	6.21	0.94	12
	Negative Feedback	punishment	5.78	1.23	28	7.40	1.52	32	6.87	0.85	16	6.42	0.95	12
		reward	5.71	1.11	28	7.41	1.51	32	6.87	0.84	16	6.45	0.85	12
		neutral	5.62	1.23	30	7.33	1.50	32	6.80	0.87	16	6.41	0.93	12
	Feedback Combined	punishment	5.58	1.18	30	7.30	1.54	32	6.75	0.87	16	6.30	0.97	12
		reward	5.59	1.16	30	7.31	1.53	32	6.74	0.86	16	6.32	0.94	12
		neutral	5.49	1.23	30	7.24	1.53	32	6.68	0.87	16	6.26	0.93	12
Pupil Dilation (mm)	Positive Feedback	punishment	0.002	0.074	30	-0.014	0.081	32	-0.017	0.063	16	-0.053	0.076	12
		reward	0.010	0.101	30	0.000	0.075	32	-0.004	0.057	16	-0.041	0.064	12
		neutral	0.012	0.084	30	0.012	0.053	32	-0.012	0.034	16	-0.037	0.090	12
	Negative Feedback	punishment	0.078	0.147	28	0.032	0.084	32	0.030	0.062	16	0.019	0.089	12
		reward	0.096	0.090	28	0.034	0.077	32	0.077	0.113	16	0.020	0.084	12
		neutral	0.037	0.081	30	0.021	0.064	32	0.025	0.065	16	-0.028	0.081	12
	Feedback Combined	punishment	0.011	0.072	30	0.001	0.058	32	-0.005	0.044	16	-0.035	0.069	12
		reward	0.021	0.103	30	0.009	0.070	32	0.022	0.072	16	-0.031	0.049	12
		neutral	0.015	0.073	30	0.014	0.049	32	0.001	0.036	16	-0.036	0.079	12

9.3 Normality of data distribution

Table 9-5: Kolmogorov-Smirnov goodness-of-fit test to normal distribution (K-S Z, p) for each dependant variable of the performance period per subject group. Significant differences (p ≤ 0.05) are printed in red, p = 2-tailed.

Dependant Variable per Saccade Type and Incentive Condition			Adults		Adolescents		Anxious Patients		MDD Patients	
			K-S Z	p	K-S Z	p	K-S Z	p	K-S Z	p
correct prosaccades	Frequency	punishment	0.95	0.333	1.00	0.271	0.60	0.864	0.39	0.998
		reward	0.94	0.339	1.35	0.051	0.54	0.937	0.64	0.802
		neutral	1.10	0.181	1.10	0.180	0.91	0.380	0.68	0.743
	Latency	punishment	0.60	0.869	0.79	0.559	0.63	0.824	0.74	0.643
		reward	0.61	0.857	0.79	0.556	0.94	0.338	0.57	0.896
		neutral	0.63	0.817	1.06	0.211	0.79	0.555	0.73	0.654
	Peak Velocity	punishment	1.14	0.149	1.29	0.072	0.84	0.486	0.92	0.367
		reward	1.12	0.162	1.21	0.110	0.80	0.541	0.73	0.654
		neutral	1.07	0.202	1.18	0.125	0.62	0.832	0.86	0.457
	Saccade Duration	punishment	1.14	0.146	0.86	0.445	0.84	0.485	0.78	0.569
		reward	0.92	0.370	0.74	0.636	0.65	0.799	0.97	0.308
		neutral	0.97	0.300	0.86	0.449	0.55	0.919	0.77	0.599
	Saccade Amplitude	punishment	0.79	0.559	1.00	0.275	0.85	0.461	0.78	0.575
		reward	0.67	0.762	0.69	0.726	0.71	0.692	0.47	0.980
		neutral	0.61	0.847	0.66	0.783	0.67	0.766	0.62	0.833
correct antisaccades	Frequency	punishment	0.70	0.717	0.56	0.911	1.07	0.199	0.83	0.494
		reward	0.91	0.376	0.71	0.691	0.74	0.647	0.83	0.503
		neutral	0.57	0.899	0.46	0.984	0.65	0.787	0.50	0.961
	Latency	punishment	0.73	0.667	0.96	0.311	0.83	0.504	0.76	0.610
		reward	0.66	0.781	0.66	0.781	0.54	0.929	0.68	0.739
		neutral	0.74	0.640	0.95	0.332	0.88	0.423	1.05	0.218
	Peak Velocity	punishment	0.77	0.601	1.14	0.150	0.73	0.653	1.03	0.243
		reward	0.62	0.842	0.93	0.354	0.90	0.387	0.73	0.667
		neutral	1.04	0.226	0.58	0.884	0.50	0.965	0.68	0.744
	Saccade Duration	punishment	0.90	0.392	0.68	0.736	0.70	0.719	1.35	0.052
		reward	1.29	0.070	0.90	0.396	0.68	0.740	0.96	0.319
		neutral	0.77	0.587	0.93	0.356	0.56	0.917	0.78	0.583
	Saccade Amplitude	punishment	0.81	0.535	0.69	0.730	0.84	0.486	0.96	0.311
		reward	0.88	0.423	0.76	0.614	0.81	0.528	0.49	0.968
		neutral	0.56	0.908	0.95	0.324	0.77	0.592	0.76	0.616
antisaccade direction errors	Frequency	punishment	0.58	0.891	0.65	0.798	0.95	0.324	0.65	0.795
		reward	0.73	0.655	0.66	0.780	0.86	0.455	0.52	0.947
		neutral	0.54	0.929	0.40	0.998	0.71	0.699	0.61	0.855
	Latency	punishment	0.74	0.648	0.78	0.583	1.03	0.244	0.62	0.841
		reward	0.46	0.983	1.12	0.165	0.68	0.743	0.74	0.644
		neutral	0.81	0.532	0.83	0.492	0.55	0.923	0.37	0.999
	Peak Velocity	punishment	0.49	0.969	0.93	0.353	0.96	0.320	0.73	0.665
		reward	1.81	0.003	1.68	0.007	0.61	0.844	0.65	0.798
		neutral	1.54	0.018	0.87	0.430	0.84	0.488	0.50	0.967
	Saccade Duration	punishment	0.78	0.574	0.83	0.497	0.84	0.483	0.68	0.748
		reward	0.99	0.285	0.80	0.547	0.70	0.708	0.65	0.791
		neutral	0.80	0.548	0.79	0.554	0.70	0.712	1.36	0.049
	Saccade Amplitude	punishment	0.48	0.973	0.59	0.883	0.40	0.997	0.57	0.903
		reward	0.40	0.997	1.66	0.008	0.36	1.000	0.91	0.378
		neutral	1.03	0.236	0.65	0.796	0.50	0.962	0.38	0.999
corrective saccades	Frequency	punishment	1.76	0.004	1.03	0.235	1.04	0.231	0.73	0.666
		reward	1.58	0.013	0.97	0.304	0.93	0.349	0.84	0.481
		neutral	1.26	0.084	0.77	0.593	0.73	0.653	0.84	0.477
	Latency	punishment	0.60	0.866	1.24	0.090	0.82	0.510	0.40	0.997
		reward	0.71	0.692	0.76	0.602	1.00	0.270	0.76	0.604
		neutral	0.68	0.748	0.91	0.376	0.56	0.912	0.72	0.673
	Peak Velocity	punishment	1.30	0.068	0.61	0.845	1.19	0.118	0.32	1.000
		reward	1.26	0.083	1.70	0.006	0.67	0.756	1.01	0.257
		neutral	0.89	0.413	0.85	0.460	0.70	0.709	0.46	0.983
	Saccade Duration	punishment	1.25	0.089	1.52	0.020	0.70	0.703	0.58	0.895
		reward	1.59	0.013	1.49	0.024	0.77	0.601	1.02	0.246
		neutral	2.14	0.000	1.61	0.011	1.38	0.044	0.65	0.792
	Saccade Amplitude	punishment	0.76	0.607	0.55	0.925	0.52	0.952	0.49	0.969
		reward	0.78	0.577	1.05	0.220	0.68	0.748	0.67	0.767
		neutral	2.15	0.000	0.69	0.725	1.11	0.170	0.48	0.975

Table 9-6: Kolmogorov-Smirnov goodness-of-fit test to normal distribution (K-S Z, p) for each dependant variable of the outcome notification period per subject group. Significant differences ($p \leq 0.05$) are printed in red, p = 2-tailed.

Dependant Variable per Feedback Type and Incentive Condition			Adults		Adolescents		Anxious Patients		MDD Patients	
			K-S Z	p	K-S Z	p	K-S Z	p	K-S Z	p
Fixation Duration	Positive Feedback	punishment	0.87	0.442	0.53	0.940	0.53	0.945	0.69	0.721
		reward	0.80	0.536	0.66	0.777	0.46	0.983	0.41	0.996
		neutral	0.46	0.983	0.60	0.869	0.56	0.915	0.50	0.964
	Negative Feedback	punishment	0.51	0.959	0.56	0.910	0.50	0.962	0.39	0.998
		reward	0.80	0.540	0.80	0.546	0.51	0.955	0.75	0.625
		neutral	0.92	0.370	0.51	0.955	0.43	0.993	0.44	0.989
	Feedback Combined	punishment	0.66	0.770	0.47	0.980	0.38	0.999	0.46	0.986
		reward	0.68	0.752	0.62	0.835	0.41	0.996	0.55	0.923
		neutral	0.66	0.779	0.69	0.734	0.53	0.939	0.53	0.943
Pupil Diameter	Positive Feedback	punishment	0.49	0.970	0.49	0.968	0.54	0.931	0.57	0.906
		reward	0.36	0.999	0.52	0.952	0.50	0.963	0.57	0.905
		neutral	0.49	0.973	0.49	0.967	0.41	0.995	0.61	0.852
	Negative Feedback	punishment	0.33	1.000	0.63	0.819	0.55	0.919	0.50	0.961
		reward	0.51	0.958	0.64	0.813	0.41	0.996	0.43	0.993
		neutral	0.41	0.996	0.62	0.839	0.49	0.972	0.49	0.969
	Feedback Combined	punishment	0.45	0.987	0.47	0.982	0.54	0.933	0.53	0.943
		reward	0.43	0.993	0.48	0.975	0.53	0.940	0.53	0.942
		neutral	0.48	0.977	0.53	0.943	0.51	0.956	0.60	0.869
Pupil Dilation	Positive Feedback	punishment	0.34	1.000	0.99	0.282	0.72	0.677	0.40	0.997
		reward	1.21	0.107	0.59	0.871	0.48	0.977	0.70	0.707
		neutral	0.78	0.578	0.76	0.615	0.57	0.906	0.46	0.984
	Negative Feedback	punishment	0.88	0.421	0.89	0.409	0.54	0.932	0.55	0.922
		reward	0.73	0.657	0.92	0.367	0.99	0.280	0.50	0.962
		neutral	0.59	0.881	0.49	0.968	0.59	0.876	0.37	0.999
	Feedback Combined	punishment	0.44	0.990	0.47	0.981	0.50	0.965	0.39	0.998
		reward	1.07	0.199	0.38	0.999	0.92	0.363	0.49	0.972
		neutral	0.52	0.952	0.58	0.896	0.74	0.652	0.51	0.959

9.4 Homogeneity of variance

Table 9-7: Levene test for homogeneity of variance ($F_{df1/df2}$, p) for dependant variables of the performance period, per study sample investigated. Significant differences ($p \leq 0.05$) are printed in red, p = 2-tailed.

Dependant Variable per Saccade Type and Incentive Condition			Developmental study		Clinical study	
			F	p	F	p
correct prosaccades	Frequency	punishment	$F_{1,60} = 7.39$	0.009	$F_{2,57} = 2.41$	0.099
		reward	$F_{1,60} = 0.18$	0.674	$F_{2,57} = 0.39$	0.677
		neutral	$F_{1,60} = 4.75$	0.033	$F_{2,57} = 1.93$	0.155
	Latency	punishment	$F_{1,60} = 15.44$	0.000	$F_{2,57} = 1.83$	0.170
		reward	$F_{1,60} = 5.91$	0.018	$F_{2,57} = 0.24$	0.789
		neutral	$F_{1,60} = 8.24$	0.006	$F_{2,57} = 2.08$	0.134
	Peak Velocity	punishment	$F_{1,60} = 2.54$	0.116	$F_{2,57} = 2.64$	0.080
		reward	$F_{1,60} = 4.69$	0.034	$F_{2,57} = 1.87$	0.164
		neutral	$F_{1,60} = 3.11$	0.083	$F_{2,57} = 2.53$	0.088
	Saccade Duration	punishment	$F_{1,60} = 0.09$	0.770	$F_{2,57} = 1.22$	0.302
		reward	$F_{1,60} = 0.09$	0.759	$F_{2,57} = 0.65$	0.524
		neutral	$F_{1,60} = 0.06$	0.803	$F_{2,57} = 4.05$	0.023
	Saccade Amplitude	punishment	$F_{1,60} = 2.79$	0.100	$F_{2,57} = 0.75$	0.477
		reward	$F_{1,60} = 2.05$	0.157	$F_{2,57} = 2.10$	0.131
		neutral	$F_{1,60} = 6.03$	0.017	$F_{2,57} = 0.94$	0.396
correct antisaccades	Frequency	punishment	$F_{1,60} = 0.00$	0.985	$F_{2,57} = 0.62$	0.543
		reward	$F_{1,60} = 0.00$	0.948	$F_{2,57} = 0.13$	0.874
		neutral	$F_{1,60} = 4.13$	0.047	$F_{2,57} = 0.81$	0.451
	Latency	punishment	$F_{1,60} = 3.62$	0.062	$F_{2,57} = 2.64$	0.080
		reward	$F_{1,60} = 0.18$	0.674	$F_{2,57} = 0.25$	0.783
		neutral	$F_{1,60} = 0.70$	0.406	$F_{2,57} = 1.23$	0.301
	Peak Velocity	punishment	$F_{1,60} = 1.78$	0.187	$F_{2,57} = 3.41$	0.040
		reward	$F_{1,60} = 1.82$	0.182	$F_{2,57} = 4.20$	0.020
		neutral	$F_{1,60} = 0.84$	0.363	$F_{2,57} = 0.00$	0.996
	Saccade Duration	punishment	$F_{1,60} = 0.68$	0.412	$F_{2,57} = 1.71$	0.190
		reward	$F_{1,60} = 0.01$	0.916	$F_{2,57} = 0.30$	0.745
		neutral	$F_{1,60} = 0.87$	0.354	$F_{2,57} = 1.11$	0.336
	Saccade Amplitude	punishment	$F_{1,60} = 0.28$	0.597	$F_{2,57} = 0.49$	0.617
		reward	$F_{1,60} = 0.42$	0.517	$F_{2,57} = 1.90$	0.159
		neutral	$F_{1,60} = 0.20$	0.655	$F_{2,57} = 0.18$	0.836
antisaccade direction errors	Frequency	punishment	$F_{1,60} = 5.84$	0.019	$F_{2,57} = 0.33$	0.723
		reward	$F_{1,60} = 1.13$	0.292	$F_{2,57} = 0.71$	0.496
		neutral	$F_{1,60} = 3.68$	0.060	$F_{2,57} = 1.16$	0.319
	Latency	punishment	$F_{1,53} = 0.57$	0.453	$F_{2,56} = 0.25$	0.779
		reward	$F_{1,53} = 0.72$	0.399	$F_{2,56} = 1.74$	0.185
		neutral	$F_{1,53} = 0.02$	0.889	$F_{2,56} = 0.30$	0.743
	Peak Velocity	punishment	$F_{1,53} = 0.50$	0.483	$F_{2,56} = 0.48$	0.620
		reward	$F_{1,53} = 1.43$	0.237	$F_{2,56} = 7.77$	0.001
		neutral	$F_{1,53} = 2.30$	0.135	$F_{2,56} = 2.49$	0.092
	Saccade Duration	punishment	$F_{1,53} = 2.58$	0.114	$F_{2,56} = 1.04$	0.361
		reward	$F_{1,53} = 0.10$	0.752	$F_{2,56} = 1.76$	0.182
		neutral	$F_{1,53} = 0.47$	0.494	$F_{2,56} = 1.66$	0.200
	Saccade Amplitude	punishment	$F_{1,53} = 3.34$	0.073	$F_{2,56} = 1.71$	0.191
		reward	$F_{1,53} = 0.85$	0.359	$F_{2,56} = 0.63$	0.534
		neutral	$F_{1,53} = 1.53$	0.221	$F_{2,56} = 3.67$	0.032
corrective saccades	Frequency	punishment	$F_{1,53} = 0.37$	0.547	$F_{2,56} = 3.38$	0.041
		reward	$F_{1,53} = 0.66$	0.419	$F_{2,56} = 1.01$	0.370
		neutral	$F_{1,53} = 0.55$	0.462	$F_{2,56} = 1.39$	0.257
	Latency	punishment	$F_{1,48} = 5.73$	0.021	$F_{2,52} = 0.06$	0.946
		reward	$F_{1,48} = 3.17$	0.081	$F_{2,52} = 0.05$	0.956
		neutral	$F_{1,48} = 6.10$	0.017	$F_{2,52} = 0.39$	0.678
	Peak Velocity	punishment	$F_{1,48} = 7.32$	0.009	$F_{2,52} = 4.72$	0.013
		reward	$F_{1,48} = 0.00$	0.979	$F_{2,52} = 2.52$	0.090
		neutral	$F_{1,48} = 0.04$	0.849	$F_{2,52} = 2.31$	0.109
	Saccade Duration	punishment	$F_{1,48} = 0.05$	0.831	$F_{2,52} = 0.57$	0.567
		reward	$F_{1,48} = 1.26$	0.267	$F_{2,52} = 0.32$	0.729
		neutral	$F_{1,48} = 0.40$	0.532	$F_{2,52} = 2.20$	0.121
	Saccade Amplitude	punishment	$F_{1,48} = 0.14$	0.713	$F_{2,52} = 0.75$	0.478
		reward	$F_{1,48} = 0.25$	0.621	$F_{2,52} = 1.61$	0.209
		neutral	$F_{1,48} = 2.87$	0.097	$F_{2,52} = 2.22$	0.119

Table 9-8: Levene test for homogeneity of variance ($F_{df1/df2}$, p) for dependant variables of the outcome notification period, per study sample investigated. Significant differences ($p \leq 0.05$) are printed in red, p = 2-tailed.

Dependant Variable per Feedback Type and Incentive Condition			Developmental study		Clinical study	
			F	p	F	p
Fixation Duration	Positive Feedback	punishment	$F_{1,60} = 0.65$	0.422	$F_{2,57} = 0.25$	0.781
		reward	$F_{1,60} = 0.40$	0.530	$F_{2,57} = 0.12$	0.885
		neutral	$F_{1,60} = 0.77$	0.384	$F_{2,57} = 0.31$	0.738
	Negative Feedback	punishment	$F_{1,57} = 0.04$	0.846	$F_{2,57} = 1.81$	0.174
		reward	$F_{1,57} = 0.63$	0.430	$F_{2,57} = 0.76$	0.473
		neutral	$F_{1,57} = 0.62$	0.434	$F_{2,57} = 2.26$	0.113
	Feedback Combined	punishment	$F_{1,60} = 0.52$	0.472	$F_{2,57} = 0.53$	0.589
		reward	$F_{1,60} = 0.18$	0.674	$F_{2,57} = 3.32$	0.043
		neutral	$F_{1,60} = 0.38$	0.539	$F_{2,57} = 0.98$	0.383
Pupil Diameter	Positive Feedback	punishment	$F_{1,60} = 1.27$	0.265	$F_{2,57} = 2.56$	0.086
		reward	$F_{1,60} = 1.59$	0.212	$F_{2,57} = 2.75$	0.072
		neutral	$F_{1,60} = 0.92$	0.341	$F_{2,57} = 2.70$	0.076
	Negative Feedback	punishment	$F_{1,57} = 1.18$	0.282	$F_{2,57} = 2.85$	0.066
		reward	$F_{1,57} = 1.33$	0.254	$F_{2,57} = 3.12$	0.052
		neutral	$F_{1,57} = 0.91$	0.345	$F_{2,57} = 2.91$	0.063
	Feedback Combined	punishment	$F_{1,60} = 1.22$	0.274	$F_{2,57} = 2.66$	0.079
		reward	$F_{1,60} = 1.57$	0.215	$F_{2,57} = 2.95$	0.061
		neutral	$F_{1,60} = 0.94$	0.337	$F_{2,57} = 2.95$	0.060
Pupil Dilation	Positive Feedback	punishment	$F_{1,60} = 0.04$	0.847	$F_{2,57} = 0.39$	0.679
		reward	$F_{1,60} = 0.15$	0.698	$F_{2,57} = 0.85$	0.434
		neutral	$F_{1,60} = 2.80$	0.099	$F_{2,57} = 7.80$	0.001
	Negative Feedback	punishment	$F_{1,57} = 1.99$	0.164	$F_{2,57} = 0.36$	0.698
		reward	$F_{1,57} = 0.66$	0.419	$F_{2,57} = 0.28$	0.757
		neutral	$F_{1,57} = 0.04$	0.848	$F_{2,57} = 0.32$	0.728
	Feedback Combined	punishment	$F_{1,60} = 1.55$	0.218	$F_{2,57} = 1.39$	0.256
		reward	$F_{1,60} = 0.34$	0.564	$F_{2,57} = 0.73$	0.488
		neutral	$F_{1,60} = 3.58$	0.063	$F_{2,57} = 4.55$	0.015

9.5 Results Developmental Study

9.5.1 Self-reports

Table 9-9: Proportion of responses per answer category for each question of the Debriefing Questionnaire performed after completion of the RST per group (1 = "not at all"; 2 = "a little"; 3 = "very"; 4 = "extremely"); and results of the Mann-Whitney test (Z-value, p) for each item of the Debriefing Questionnaire. Significant group differences ($p \leq 0.05$) are printed in red, p =2-tailed.

	Rating Adults (%)				Rating Adolescents (%)				Mann-Whitney	
Item on Questionnaire	*1*	*2*	*3*	*4*	*1*	*2*	*3*	*4*	Z	p
Were you able to distinguish between gray and white?	0	10	50	40	0	13	44	44	-0.09	0.931
How difficult was the task for you?	30	65	4	0	22	70	9	0	-0.80	0.423
How much did you enjoy doing the task?	4	22	52	22	4	13	52	30	-0.82	0.414
How excited did you get when you won money?	4	22	52	22	4	26	39	30	-0.20	0.842
How nervous were you?	67	25	8	0	57	30	9	4	-0.77	0.444
How bored were you?	71	29	0	0	35	48	9	9	-2.71	0.007
Did you want to play more?	17	46	13	25	26	35	17	22	-0.38	0.704
Did you get upset when you lost 1$?	25	63	8	4	52	26	9	13	-1.02	0.305
Did you get upset when you received negative feedback?	40	40	20	0	67	13	20	0	-0.99	0.322
Did you try to guess where the star would be?	48	43	4	4	22	39	22	17	-2.44	0.015
Did the computer make mistakes?	38	46	13	4	35	39	17	9	-0.54	0.592
Was the task too slow for you?	87	9	4	0	87	13	0	0	-0.06	0.955
Was the task too fast for you?	96	4	0	0	77	18	5	0	-1.81	0.070
Did you have trouble looking at the opposite side of the star?	21	79	0	0	26	57	9	9	-0.61	0.542
How hard was it for you to stay focused?	67	29	4	0	30	48	22	0	-2.62	0.009
How tired did you get during the task?	57	39	4	0	32	55	9	5	-1.78	0.075
How angry did the task make you feel?	79	21	0	0	91	4	0	4	-1.07	0.286
How sad/depressed did the task made you feel?	96	4	0	0	96	4	0	0	-0.03	0.976
How frustrated did the task make you feel?	75	25	0	0	78	17	0	4	-0.17	0.862
Did you have trouble sitting still?	74	22	0	4	39	43	17	0	-2.36	0.018
Do you think the game was rigged?	96	4	0	0	70	17	0	13	-2.35	0.019
Did your eyes hurt?	46	54	0	0	39	26	22	13	-1.62	0.105
Did the computer say you were wrong when you were right?	38	42	17	4	45	36	5	14	-0.37	0.714
Did the computer say you were right when you were wrong?	80	20	0	0	100	0	0	0	-1.71	0.087
Did you care about the meaning of the central sign?	17	42	38	4	22	17	35	26	-1.31	0.190
Were you excited when it was a +?	8	29	50	13	13	39	13	35	-0.03	0.973
How rewarding is money to you?	0	0	60	40	8	15	46	31	-1.03	0.303

9.5.2 Performance period

Table 9-10: Summary of main effects and interactions ($F_{df/dferror}$, p) of the Analysis of Variance for each dependant variable per saccade type. Significant differences (p ≤ 0.05 resp. ≤ 0.025 for variables with inhomogeneous variances) are printed in red.

Dependant Variable per Saccade Type		Type	Type by Age	Incentives	Incentives by Age	Incentives by Type	Incentives by Type by Age	Age
correct saccades	Frequency	$F_{1,60}$ = 166.39 p = 0.000	$F_{1,60}$ = 8.68 p = 0.005	$F_{2,59}$ = 18.99 p = 0.000	$F_{2,59}$ = 0.21 p = 0.809	$F_{2,59}$ = 18.43 p = 0.000	$F_{2,59}$ = 0.10 p = 0.907	$F_{1,60}$ = 11.32 p = 0.001
	Latency	$F_{1,60}$ = 450.61 p = 0.000	$F_{1,60}$ = 6.60 p = 0.013	$F_{2,59}$ = 2.71 p = 0.075	$F_{2,59}$ = 1.09 p = 0.345	$F_{2,59}$ = 0.58 p = 0.563	$F_{2,59}$ = 0.04 p = 0.964	$F_{1,60}$ = 8.48 p = 0.005
	Peak Velocity	$F_{1,60}$ = 21.24 p = 0.000	$F_{1,60}$ = 6.33 p = 0.015	$F_{2,59}$ = 2.38 p = 0.102	$F_{2,59}$ = 0.55 p = 0.581	$F_{2,59}$ = 0.23 p = 0.792	$F_{2,59}$ = 0.56 p = 0.576	$F_{1,60}$ = 2.02 p = 0.160
	Saccade Duration	$F_{1,60}$ = 61.23 p = 0.000	$F_{1,60}$ = 0.00 p = 0.997	$F_{2,59}$ = 0.59 p = 0.556	$F_{2,59}$ = 0.16 p = 0.851	$F_{2,59}$ = 0.38 p = 0.686	$F_{2,59}$ = 0.32 p = 0.727	$F_{1,60}$ = 0.18 p = 0.674
	Saccade Amplitude	$F_{1,60}$ = 45.50 p = 0.000	$F_{1,60}$ = 1.12 p = 0.294	$F_{2,59}$ = 2.48 p = 0.092	$F_{2,59}$ = 0.18 p = 0.833	$F_{2,59}$ = 0.44 p = 0.647	$F_{2,59}$ = 0.36 p = 0.702	$F_{1,60}$ = 1.20 p = 0.278
antisaccade direction errors	Frequency			$F_{2,59}$ = 14.17 p = 0.000	$F_{2,59}$ = 0.03 p = 0.970			$F_{1,60}$ = 10.85 p = 0.002
	Latency			$F_{2,52}$ = 1.92 p = 0.157	$F_{2,52}$ = 0.63 p = 0.535			$F_{1,53}$ = 1.51 p = 0.224
	Peak Velocity			$F_{2,52}$ = 3.44 p = 0.040	$F_{2,52}$ = 0.26 p = 0.772			$F_{1,53}$ = 1.50 p = 0.226
	Saccade Duration			$F_{2,52}$ = 0.01 p = 0.992	$F_{2,52}$ = 0.23 p = 0.794			$F_{1,53}$ = 0.43 p = 0.512
	Saccade Amplitude			$F_{2,52}$ = 0.76 p = 0.474	$F_{2,52}$ = 0.68 p = 0.509			$F_{1,53}$ = 2.26 p = 0.139
corrective saccades	Frequency			$F_{2,52}$ = 0.94 p = 0.398	$F_{2,52}$ = 0.42 p = 0.658			$F_{1,53}$ = 3.10 p = 0.084
	Latency			$F_{2,47}$ = 0.85 p = 0.435	$F_{2,47}$ = 4.85 p = 0.015			$F_{1,48}$ = 22.05 p = 0.000
	Peak Velocity			$F_{2,47}$ = 4.34 p = 0.019	$F_{2,47}$ = 0.43 p = 0.656			$F_{1,48}$ = 1.71 p = 0.197
	Saccade Duration			$F_{2,47}$ = 1.46 p = 0.243	$F_{2,47}$ = 0.10 p = 0.907			$F_{1,48}$ = 0.21 p = 0.653
	Saccade Amplitude			$F_{2,47}$ = 4.55 p = 0.016	$F_{2,47}$ = 3.40 p = 0.042			$F_{1,48}$ = 2.00 p = 0.164

Table 9-11: Post-hoc within-group analysis (paired-sample t-test T_{df} or Wilcoxon Z; significance p; effect size d_z for t-tests) for all dependant variables per saccade type showing an incentive-related modulation in the Analysis of Variance, per within-group comparison, and subject group. Significant differences ($p \leq 0.05/3 = 0.0167$) are printed in red, p =1-tailed. rew = reward condition, pun = punishment condition; neu = neutral condition.

Comparison between two Incentive Conditions per Saccade Type and Dependant Variable			All subjects			Adults			Adolescents		
			T or Z	p	d_z	T or Z	p	d_z	T or Z	p	d_z
correct responses	Latency	rew - pun	$T_{61} = -2.68$	0.005	-0.34	$T_{29} = -1.56$	0.065	-0.28	$T_{31} = -2.23$	0.017	-0.39
		rew - neu	$T_{61} = -0.36$	0.360	-0.05	$T_{29} = -0.27$	0.393	-0.05	$T_{31} = -0.24$	0.406	-0.04
		pun - neu	$T_{61} = 2.46$	0.008	0.31	$T_{29} = 0.95$	0.175	0.17	$T_{31} = 2.37$	0.012	0.42
	Peak velocity	rew - pun	$T_{61} = 1.36$	0.090	0.17	$T_{29} = 1.47$	0.076	0.27	$T_{31} = 0.43$	0.337	0.08
		rew - neu	$T_{61} = 2.91$	0.003	0.37	$T_{29} = 1.35$	0.094	0.25	$T_{31} = 2.67$	0.006	0.47
		pun - neu	$T_{61} = 1.54$	0.065	0.20	$T_{29} = -0.10$	0.460	-0.02	$T_{31} = 2.34$	0.013	0.41
correct prosaccades	Frequency	rew - pun	$T_{61} = 4.03$	0.000	0.51	$T_{29} = 2.69$	0.006	0.49	$T_{31} = 3.00$	0.003	0.53
		rew - neu	$T_{61} = 3.62$	0.000	0.46	$T_{29} = 2.59$	0.007	0.47	$T_{31} = 2.50$	0.009	0.44
		pun - neu	$T_{61} = -1.46$	0.075	-0.19	$T_{29} = -1.18$	0.124	-0.21	$T_{31} = -0.87$	0.195	-0.15
	Latency	rew - pun	$T_{61} = -2.10$	0.020	-0.27	$T_{29} = -0.42$	0.337	-0.08	$T_{31} = -2.42$	0.011	-0.43
		rew - neu	$T_{61} = -0.68$	0.251	-0.09	$T_{29} = -0.24$	0.405	-0.04	$T_{31} = -0.76$	0.226	-0.13
		pun - neu	$T_{61} = 0.94$	0.177	0.12	$T_{29} = 0.03$	0.489	0.01	$T_{31} = 1.29$	0.103	0.23
	Peak velocity	rew - pun	$T_{61} = 0.38$	0.351	0.05	$T_{29} = 1.57$	0.064	0.29	$T_{31} = -1.31$	0.100	-0.23
		rew - neu	$T_{61} = 2.33$	0.011	0.30	$T_{29} = 1.58$	0.063	0.29	$T_{31} = 1.71$	0.049	0.30
		pun - neu	$T_{61} = 1.48$	0.072	0.19	$T_{29} = -0.47$	0.322	-0.09	$T_{31} = 2.65$	0.006	0.47
correct antisaccades	Frequency	rew - pun	$T_{61} = -1.20$	0.117	-0.15	$T_{29} = -0.85$	0.201	-0.16	$T_{31} = -0.89$	0.189	-0.16
		rew - neu	$T_{61} = 4.85$	0.000	0.62	$T_{29} = 3.45$	0.001	0.63	$T_{31} = 3.40$	0.001	0.60
		pun - neu	$T_{61} = 5.88$	0.000	0.75	$T_{29} = 4.33$	0.000	0.79	$T_{31} = 4.10$	0.000	0.72
	Latency	rew - pun	$T_{61} = -1.72$	0.045	-0.22	$T_{29} = -0.79$	0.217	-0.14	$T_{31} = -1.52$	0.069	-0.27
		rew - neu	$T_{61} = -1.47$	0.074	-0.19	$T_{29} = -1.41$	0.085	-0.26	$T_{31} = -1.02$	0.157	-0.18
		pun - neu	$T_{61} = -0.33$	0.372	-0.04	$T_{29} = -0.80$	0.214	-0.15	$T_{31} = -0.04$	0.485	-0.01
	Peak velocity	rew - pun	$T_{61} = 0.88$	0.191	0.11	$T_{29} = 0.77$	0.222	0.14	$T_{31} = 0.61$	0.274	0.11
		rew - neu	$T_{61} = 1.43$	0.079	0.18	$T_{29} = 0.80$	0.214	0.15	$T_{31} = 1.18$	0.124	0.21
		pun - neu	$T_{61} = 0.63$	0.265	0.08	$T_{29} = 0.33$	0.373	0.06	$T_{31} = 0.54$	0.298	0.09
antisaccade direction errors	Frequency	rew - pun	$T_{61} = 0.59$	0.278	0.08	$T_{29} = 0.30$	0.383	0.05	$T_{31} = 0.51$	0.307	0.09
		rew - neu	$T_{61} = -4.71$	0.000	-0.60	$T_{29} = -3.64$	0.001	-0.66	$T_{31} = -3.09$	0.002	-0.55
		pun - neu	$T_{61} = -5.33$	0.000	-0.68	$T_{29} = -4.42$	0.000	-0.81	$T_{31} = -3.41$	0.001	-0.60
	Latency	rew - pun	$T_{55} = 1.65$	0.052	0.22	$T_{24} = 0.15$	0.441	0.03	$T_{30} = 1.98$	0.029	0.36
		rew - neu	$T_{55} = 2.35$	0.011	0.31	$T_{23} = 0.64$	0.265	0.13	$T_{31} = 2.43$	0.010	0.43
		pun - neu	$T_{57} = 0.75$	0.228	0.10	$T_{26} = 0.89$	0.191	0.17	$T_{30} = 0.13$	0.448	0.02
	Peak velocity	rew - pun	$Z = -1.42$	0.077		$Z = -0.31$	0.378		$Z = -1.67$	0.048	
		rew - neu	$Z = -2.48$	0.007		$Z = -1.17$	0.121		$Z = -2.15$	0.016	
		pun - neu	$Z = -0.96$	0.169		$Z = -1.21$	0.113		$Z = -0.05$	0.480	
corrective saccades	Latency	rew - pun	$T_{51} = 0.11$	0.456	0.02	$T_{22} = 1.14$	0.133	0.24	$T_{28} = -0.40$	0.347	-0.07
		rew - neu	$T_{52} = -1.29$	0.101	-0.18	$T_{23} = 1.71$	0.050	0.35	$T_{28} = -3.12$	0.002	-0.58
		pun - neu	$T_{53} = -1.58$	0.060	-0.22	$T_{24} = 0.24$	0.406	0.05	$T_{28} = -1.76$	0.045	-0.33
	Peak velocity	rew - pun	$Z = -1.27$	0.102		$T_{22} = 0.24$	0.405	0.05	$Z = -0.24$	0.406	
		rew - neu	$Z = -2.91$	0.002		$T_{23} = 3.90$	0.000	0.80	$Z = -1.14$	0.128	
		pun - neu	$Z = -1.33$	0.091		$T_{24} = 1.26$	0.111	0.25	$Z = -1.16$	0.124	
	Saccade amplitude	rew - pun	$Z = -2.14$	0.016		$Z = -3.19$	0.001		$T_{28} = 0.29$	0.387	0.05
		rew - neu	$Z = -1.53$	0.063		$Z = -2.71$	0.003		$T_{28} = 0.07$	0.472	0.01
		pun - neu	$Z = -0.31$	0.380		$Z = -0.17$	0.431		$T_{28} = -0.53$	0.299	-0.10

9.5.3 Outcome notification period

Table 9-12: Summary of main effects and interactions ($F_{df/dferror}$; p) of the Analysis of Variance for each dependant variable analyzed during the outcome notification period. Significant differences ($p \leq 0.05$) are printed in red.

Dependant Variable per Condition	Feedback	Feedback by Age	Incentives	Incentives by Age	Feedback by Incentives	Feedback by Incentives by Age	Age
Fixation Duration	$F_{1,57} = 19.20$ p = 0.000	$F_{1,57} = 2.12$ p = 0.151	$F_{2,56} = 0.28$ p = 0.754	$F_{2,56} = 0.24$ p = 0.789	$F_{2,56} = 2.08$ p = 0.134	$F_{2,56} = 0.14$ p = 0.870	$F_{1,57} = 0.79$ p = 0.377
Pupil Diameter	$F_{1,57} = 79.80$ p = 0.000	$F_{1,57} = 3.65$ p = 0.061	$F_{2,56} = 23.41$ p = 0.000	$F_{2,56} = 3.43$ p = 0.039	$F_{2,56} = 4.22$ p = 0.020	$F_{2,56} = 1.89$ p = 0.160	$F_{1,57} = 24.57$ p = 0.000
Pupil Dilation	$F_{1,57} = 20.74$ p = 0.000	$F_{1,57} = 0.99$ p = 0.324	$F_{2,56} = 3.06$ p = 0.055	$F_{2,56} = 2.40$ p = 0.100	$F_{2,56} = 4.96$ p = 0.010	$F_{2,56} = 0.77$ p = 0.468	$F_{1,57} = 3.61$ p = 0.063

Table 9-13: Post-hoc within-group analysis (paired-sample t-test Tdf; significance p; effect size d_z) for all dependant variables showing an incentive-related modulation in the Analysis of Variance, per feedback type, within-group comparison, and subject group. Significant differences ($p \leq 0.05/3 = 0.0167$) are printed in red, p =1-tailed. rew = reward condition, pun = punishment condition; neu = neutral condition.

Comparison between Incentive Conditions per Feedback Type and Dependant Variable			All subjects			Adults			Adolescents		
			T	p	d_z	T	p	d_z	T	p	d_z
Pupil Diameter	Positive Feedback	rew - pun	$T_{61} = 1.41$	0.081	0.18	$T_{29} = 0.67$	0.255	0.21	$T_{31} = 1.37$	0.091	0.04
		rew - neu	$T_{61} = 4.59$	0.000	0.58	$T_{29} = 3.66$	0.000	0.85	$T_{31} = 2.80$	0.004	0.59
		pun - neu	$T_{61} = 3.95$	0.000	0.50	$T_{29} = 3.95$	0.000	0.77	$T_{31} = 1.89$	0.034	0.40
	Negative Feedback	rew - pun	$T_{58} = 0.96$	0.169	0.13	$T_{26} = 1.09$	0.143	0.12	$T_{31} = 0.22$	0.413	0.24
		rew - neu	$T_{59} = 5.35$	0.000	0.69	$T_{27} = 4.47$	0.000	0.67	$T_{31} = 3.34$	0.001	0.49
		pun - neu	$T_{59} = 4.47$	0.000	0.58	$T_{27} = 4.06$	0.000	0.72	$T_{31} = 2.29$	0.014	0.33
	Feedback Combined	rew - pun	$T_{61} = 0.95$	0.173	0.12	$T_{29} = 0.66$	0.258	0.12	$T_{31} = 0.69$	0.246	0.12
		rew - neu	$T_{61} = 5.29$	0.000	0.67	$T_{29} = 4.17$	0.000	0.76	$T_{31} = 3.29$	0.001	0.58
		pun - neu	$T_{61} = 5.21$	0.000	0.66	$T_{29} = 5.17$	0.000	0.94	$T_{31} = 2.63$	0.007	0.47
Pupil Dilation	Positive Feedback	rew - pun	$T_{61} = 1.44$	0.077	0.18	$T_{29} = 0.73$	0.235	0.13	$T_{31} = 1.30$	0.101	0.23
		rew - neu	$T_{61} = -0.84$	0.201	-0.11	$T_{29} = -0.10$	0.461	-0.02	$T_{31} = -1.29$	0.104	-0.23
		pun - neu	$T_{61} = -2.31$	0.012	-0.29	$T_{29} = -1.07$	0.147	-0.20	$T_{31} = -2.07$	0.024	-0.37
	Negative Feedback	rew - pun	$T_{58} = 1.22$	0.114	0.16	$T_{26} = 1.84$	0.038	0.35	$T_{31} = 0.10$	0.462	0.02
		rew - neu	$T_{59} = 2.99$	0.002	0.39	$T_{27} = 3.19$	0.002	0.60	$T_{31} = 0.96$	0.173	0.17
		pun - neu	$T_{59} = 1.46$	0.074	0.19	$T_{27} = 1.28$	0.105	0.24	$T_{31} = 0.70$	0.244	0.12
	Feedback Combined	rew - pun	$T_{61} = 1.23$	0.112	0.16	$T_{29} = 0.83$	0.208	0.15	$T_{31} = 0.91$	0.184	0.16
		rew - neu	$T_{61} = 0.00$	0.499	0.00	$T_{29} = 0.40$	0.347	0.07	$T_{31} = -0.56$	0.290	-0.10
		pun - neu	$T_{61} = -1.36$	0.089	-0.17	$T_{29} = -0.43$	0.336	-0.08	$T_{31} = -1.44$	0.079	-0.26

9.6 Results Clinical Study

9.6.1 Self-reports

Table 9-14: Proportion of responses per answer category for each question of the Debriefing Questionnaire performed after completion of the RST per group (1 = "not at all"; 2 = "a little"; 3 = "very"; 4 = "extremely"); and results of the Kruskal-Wallis test (χ^2-value, df, p) for each item of the Debriefing Questionnaire. Significant group differences ($p \leq 0.05$) are printed in red.

	Rating Adolescents (%)				Rating Anxiety (%)				Rating MDD (%)				Kruskal Wallis-test		
Item on Questionnaire	*1*	*2*	*3*	*4*	*1*	*2*	*3*	*4*	*1*	*2*	*3*	*4*	χ^2	df	p
Were you able to distinguish between gray and white?	0	13	44	44	0	11	44	44	10	20	50	20	2.57	2	0.276
How difficult was the task for you?	22	70	9	0	25	67	8	0	30	50	20	0	0.05	2	0.976
How much did you enjoy doing the task?	4	13	52	30	0	17	42	42	0	30	50	20	1.31	2	0.520
How excited did you get when you won money?	4	26	39	30	0	25	33	42	0	20	30	50	1.20	2	0.549
How nervous were you?	57	30	9	4	33	58	8	0	30	50	10	10	2.06	2	0.357
How bored were you during the task?	35	48	9	9	73	27	0	0	40	60	0	0	5.20	2	0.074
Did you want to play more?	26	35	17	22	17	17	33	33	40	20	10	30	1.64	2	0.440
Did you get upset when you lost 1$?	52	26	9	13	42	25	33	0	20	70	10	0	0.72	2	0.696
Did you get upset when you received negative feedback?	67	13	20	0	22	44	33	0	10	80	10	0	4.79	2	0.091
Did you try to guess where the star would be?	22	39	22	17	25	33	33	8	20	40	10	30	0.20	2	0.905
Did the computer make mistakes?	35	39	17	9	42	42	8	8	40	40	10	10	0.32	2	0.853
Was the task too slow for you?	87	13	0	0	83	17	0	0	80	20	0	0	0.27	2	0.875
Was the task too fast for you?	77	18	5	0	67	33	0	0	70	30	0	0	0.34	2	0.843
Did you have trouble looking at the opposite side of the star?	26	57	9	9	17	67	17	0	30	50	20	0	0.16	2	0.922
How hard was it for you to stay focused?	30	48	22	0	42	50	8	0	40	40	10	10	0.84	2	0.656
How tired did you get during the task?	32	55	9	5	0	100	0	0	40	60	0	0	3.16	2	0.206
How angry did the task make you feel?	91	4	0	4	67	25	8	0	70	30	0	0	3.35	2	0.187
How sad did the task made you feel?	96	4	0	0	75	25	0	0	70	20	10	0	4.63	2	0.099
How frustrated did the task make you feel?	78	17	0	4	58	33	8	0	60	30	10	0	1.81	2	0.405
Did you have trouble sitting still?	39	43	17	0	33	67	0	0	30	70	0	0	0.11	2	0.948
Do you think the game was rigged?	70	17	0	13	67	25	8	0	70	20	0	10	0.01	2	0.996
Did your eyes hurt?	39	26	22	13	17	42	33	8	20	70	0	10	1.04	2	0.594
Did the computer say you were wrong when you were right?	45	36	5	14	42	42	8	8	30	40	20	10	0.73	2	0.693
Did the computer say you were right when you were wrong?	100	0	0	0	75	25	0	0	80	20	0	0	3.54	2	0.170
Did you care about the meaning of the central sign?	22	17	35	26	42	8	25	25	10	50	30	10	0.80	2	0.670
Were you excited when it was a plus?	13	39	13	35	0	33	42	25	0	22	44	33	1.15	2	0.562
How rewarding is money to you?	8	15	46	31	0	13	88	0	0	30	40	30	0.36	2	0.834

9.6.2 Performance period

Table 9-15: Summary of main effects and interactions ($F_{df/dferror}$, p) of the Analysis of Variance for each dependant variable per saccade type. Significant differences ($p \leq 0.05$ resp. ≤ 0.025 for variables with inhomogeneous variances) are printed in red.

Dependant Variable per Saccade Type and Condition		Type	Type by Diagnosis	Incentives	Incentives by Diagnosis	Incentives by Type	Incentives by Type by Diagnosis	Diagnosis
correct saccades	Frequency	$F_{1,57} = 157.19$ $p = 0.000$	$F_{2,57} = 0.35$ $p = 0.703$	$F_{2,56} = 7.24$ $p = 0.002$	$F_{2,57} = 3.34$ $p = 0.043$	$F_{2,56} = 7.20$ $p = 0.002$	$F_{2,57} = 1.11$ $p = 0.338$	$F_{2,57} = 0.21$ $p = 0.815$
	Latency	$F_{1,57} = 440.75$ $p = 0.000$	$F_{2,57} = 0.24$ $p = 0.788$	$F_{2,56} = 3.59$ $p = 0.034$	$F_{2,57} = 3.14$ $p = 0.051$	$F_{2,56} = 3.58$ $p = 0.034$	$F_{2,57} = 4.13$ $p = 0.021$	$F_{2,57} = 0.63$ $p = 0.538$
	Peak Velocity	$F_{1,57} = 38.46$ $p = 0.000$	$F_{2,57} = 1.29$ $p = 0.284$	$F_{2,56} = 0.92$ $p = 0.405$	$F_{2,57} = 2.94$ $p = 0.061$	$F_{2,56} = 1.04$ $p = 0.361$	$F_{2,57} = 3.33$ $p = 0.043$	$F_{2,57} = 0.78$ $p = 0.462$
	Saccade Duration	$F_{1,57} = 26.10$ $p = 0.000$	$F_{2,57} = 0.19$ 0.824	$F_{2,56} = 0.79$ $p = 0.461$	$F_{2,57} = 1.10$ $p = 0.340$	$F_{2,56} = 1.38$ $p = 0.259$	$F_{2,57} = 1.01$ $p = 0.372$	$F_{2,57} = 0.46$ $p = 0.633$
	Saccade Amplitude	$F_{1,57} = 45.76$ $p = 0.000$	$F_{2,57} = 0.29$ $p = 0.746$	$F_{2,56} = 0.76$ $p = 0.470$	$F_{2,57} = 3.67$ $p = 0.027$	$F_{2,56} = 1.90$ $p = 0.160$	$F_{2,57} = 3.91$ $p = 0.026$	$F_{2,57} = 1.99$ $p = 0.146$
antisaccade direction errors	Frequency			$F_{2,55} = 3.24$ $p = 0.046$	$F_{2,57} = 1.61$ $p = 0.209$			$F_{2,57} = 0.24$ $p = 0.787$
	Latency			$F_{2,55} = 1.99$ $p = 0.161$	$F_{2,56} = 1.21$ $p = 0.306$			$F_{2,56} = 1.25$ $p = 0.295$
	Peak Velocity			$F_{2,55} = 1.31$ $p = 0.279$	$F_{2,56} = 2.70$ $p = 0.076$			$F_{2,56} = 0.40$ $p = 0.671$
	Saccade Duration			$F_{2,55} = 1.15$ $p = 0.325$	$F_{2,56} = 1.29$ $p = 0.284$			$F_{2,56} = 2.83$ $p = 0.068$
	Saccade Amplitude			$F_{2,55} = 1.39$ $p = 0.259$	$F_{2,56} = 0.76$ $p = 0.472$			$F_{2,56} = 1.26$ $p = 0.292$
corrective saccades	Frequency			$F_{2,55} = 0.62$ $p = 0.544$	$F_{2,56} = 1.99$ $p = 0.147$			$F_{2,56} = 2.03$ $p = 0.141$
	Latency			$F_{2,51} = 3.50$ $p = 0.038$	$F_{2,52} = 1.75$ $p = 0.185$			$F_{2,52} = 0.82$ $p = 0.446$
	Peak Velocity			$F_{2,51} = 1.20$ $p = 0.311$	$F_{2,52} = 2.18$ $p = 0.123$			$F_{2,52} = 1.70$ $p = 0.192$
	Saccade Duration			$F_{2,51} = 0.81$ $p = 0.449$	$F_{2,52} = 1.07$ $p = 0.349$			$F_{2,52} = 0.17$ $p = 0.843$
	Saccade Amplitude			$F_{2,51} = 0.82$ $p = 0.447$	$F_{2,52} = 2.64$ $p = 0.081$			$F_{2,52} = 0.78$ $p = 0.465$

Table 9-16: Summary of main effects and interactions (Fdf/dferror, p) of the Analysis of Variance for each dependant variable per saccade type when excluding the patients with MDD with a comorbid anxiety disorder. Significant differences ($p \leq 0.05$ resp. ≤ 0.025 for variables with inhomogeneous variances) are printed in red.

Dependant Variable per Saccade Type and Condition		Type	Type by Diagnosis	Incentives	Incentives by Diagnosis	Incentives by Type	Incentives by Type by Diagnosis	Diagnosis
correct saccades	Frequency	$F_{1,53} = 122.62$ 0.000	$F_{2,53} = 0.35$ 0.703	$F_{2,52} = 5.46$ 0.007	$F_{2,53} = 2.87$ 0.066	$F_{2,52} = 4.97$ 0.011	$F_{2,53} = 1.12$ 0.334	$F_{2,53} = 0.07$ 0.936
	Latency	$F_{1,53} = 348.49$ 0.000	$F_{2,53} = 0.21$ 0.813	$F_{2,52} = 4.73$ 0.013	$F_{2,53} = 6.92$ 0.002	$F_{2,52} = 4.86$ 0.012	$F_{2,53} = 5.83$ 0.005	$F_{2,53} = 1.74$ 0.185
	Peak Velocity	$F_{1,53} = 40.76$ 0.000	$F_{2,53} = 2.69$ 0.077	$F_{2,52} = 1.99$ 0.148	$F_{2,53} = 4.98$ 0.010	$F_{2,52} = 1.95$ 0.153	$F_{2,53} = 4.46$ 0.016	$F_{2,53} = 1.13$ 0.330
	Saccade Duration	$F_{1,53} = 21.99$ 0.000	$F_{2,53} = 0.09$ 0.919	$F_{2,52} = 0.84$ 0.438	$F_{2,53} = 1.06$ 0.353	$F_{2,52} = 1.13$ 0.330	$F_{2,53} = 0.90$ 0.411	$F_{2,53} = 0.57$ 0.570
	Saccade Amplitude	$F_{1,53} = 44.24$ 0.000	$F_{2,53} = 0.88$ 0.423	$F_{2,52} = 2.10$ 0.133	$F_{2,53} = 6.28$ 0.004	$F_{2,52} = 2.67$ 0.078	$F_{2,53} = 4.42$ 0.017	$F_{2,53} = 2.18$ 0.123
antisaccade direction errors	Frequency			$F_{2,52} = 2.58$ 0.085	$F_{2,53} = 1.50$ 0.232			$F_{2,53} = 0.15$ 0.859
	Latency			$F_{2,51} = 1.12$ 0.334	$F_{2,52} = 1.09$ 0.343			$F_{2,53} = 2.45$ 0.097
	Peak Velocity			$F_{2,51} = 0.92$ 0.404	$F_{2,52} = 2.55$ 0.088			$F_{2,53} = 0.51$ 0.606
	Saccade Duration			$F_{2,51} = 0.89$ 0.417	$F_{2,52} = 0.89$ 0.415			$F_{2,53} = 1.11$ 0.336
	Saccade Amplitude			$F_{2,51} = 1.63$ 0.206	$F_{2,52} = 1.09$ 0.342			$F_{2,53} = 0.33$ 0.721
corrective saccades	Frequency			$F_{2,51} = 0.75$ 0.480	$F_{2,52} = 2.13$ 0.130			$F_{2,52} = 2.17$ 0.125
	Latency			$F_{2,47} = 2.10$ 0.134	$F_{2,48} = 2.93$ 0.063			$F_{2,48} = 0.84$ 0.436
	Peak Velocity			$F_{2,47} = 1.16$ 0.322	$F_{2,48} = 1.63$ 0.207			$F_{2,48} = 1.54$ 0.225
	Saccade Duration			$F_{2,47} = 0.63$ 0.536	$F_{2,48} = 1.02$ 0.368			$F_{2,48} = 0.19$ 0.825
	Saccade Amplitude			$F_{2,47} = 0.59$ 0.556	$F_{2,48} = 2.41$ 0.101			$F_{2,48} = 0.69$ 0.508

Table 9-17: Post-hoc within group-analysis (paired-sample t-test T_{df} or Wilcoxon Z; significance p; effect size d_z for t-tests) for all dependant variables per saccade type showing an incentive-related modulation in the Analysis of Variance, per within-group comparison, and subject group. Significant differences ($p \leq 0.05/3 = 0.0167$) are printed in red, p =1-tailed. rew = reward condition, pun = punishment condition; neu = neutral condition.

Comparison between Incentive Conditions per Saccade Type and Dependant Variable			All subjects			Adolescents			Patients with Anxiety			Patients with MDD		
			T or Z	p	d_z	T or Z	p	d_z	T or Z	p	d_z	T or Z	p	d_z
correct prosaccades	Frequency	rew - pun	$T_{66} = 4.35$	0.000	0.53	$T_{31} = 3.00$	0.003	0.53	$T_{15} = 2.56$	0.011	0.64	$T_{11} = 1.80$	0.049	0.52
		rew - neu	$T_{66} = 2.89$	0.003	0.35	$T_{31} = 2.50$	0.009	0.44	$T_{15} = 1.84$	0.043	0.46	$T_{11} = 0.11$	0.457	0.03
		pun - neu	$T_{66} = -2.55$	0.007	-0.31	$T_{31} = -0.87$	0.195	-0.15	$T_{15} = -1.56$	0.070	-0.39	$T_{11} = -2.50$	0.015	-0.72
	Latency	rew - pun	$T_{66} = -2.97$	0.002	-0.36	$T_{31} = -2.42$	0.011	-0.43	$T_{15} = -0.75$	0.233	-0.19	$T_{11} = -1.35$	0.103	-0.39
		rew - neu	$T_{66} = -1.90$	0.031	-0.23	$T_{31} = -0.76$	0.226	-0.13	$T_{15} = -1.06$	0.153	-0.27	$T_{11} = -1.06$	0.156	-0.31
		pun - neu	$T_{66} = 0.59$	0.278	0.07	$T_{31} = 1.29$	0.103	0.23	$T_{15} = -0.32$	0.377	-0.08	$T_{11} = -0.03$	0.489	-0.01
	Peak velocity	rew - pun	$T_{66} = -0.40$	0.347	-0.05	$T_{31} = -1.31$	0.100	-0.23	$T_{15} = 0.22$	0.413	0.06	$T_{11} = 0.19$	0.428	0.05
		rew - neu	$T_{66} = 1.41$	0.082	0.17	$T_{31} = 1.71$	0.049	0.30	$T_{15} = -0.18$	0.429	-0.05	$T_{11} = 0.74$	0.236	0.22
		pun - neu	$T_{66} = 1.85$	0.034	0.23	$T_{31} = 2.65$	0.006	0.47	$T_{15} = -0.54$	0.300	-0.13	$T_{11} = 0.32$	0.376	0.09
	Saccade amplitude	rew - pun	$T_{66} = 0.59$	0.280	0.07	$T_{31} = 1.05$	0.151	0.19	$T_{15} = 0.17$	0.433	0.04	$T_{11} = -0.15$	0.442	-0.04
		rew - neu	$T_{66} = 2.66$	0.005	0.32	$T_{31} = 2.88$	0.004	0.51	$T_{15} = 0.38$	0.353	0.10	$T_{11} = 1.48$	0.084	0.43
		pun - neu	$T_{66} = 1.55$	0.063	0.19	$T_{31} = 1.75$	0.045	0.31	$T_{15} = 0.11$	0.457	0.03	$T_{11} = 1.12$	0.144	0.32
correct antisaccades	Frequency	rew - pun	$T_{66} = -0.43$	0.333	-0.05	$T_{31} = -0.89$	0.189	-0.16	$T_{15} = -0.01$	0.495	0.00	$T_{11} = 0.43$	0.339	0.12
		rew - neu	$T_{66} = 3.63$	0.000	0.44	$T_{31} = 3.40$	0.001	0.60	$T_{15} = 0.90$	0.190	0.23	$T_{11} = 1.45$	0.088	0.42
		pun - neu	$T_{66} = 3.72$	0.000	0.45	$T_{31} = 4.10$	0.000	0.72	$T_{15} = 0.76$	0.228	0.19	$T_{11} = 0.76$	0.233	0.22
	Latency	rew - pun	$T_{66} = -0.15$	0.440	-0.02	$T_{31} = -1.52$	0.069	-0.27	$T_{15} = -0.71$	0.243	-0.18	$T_{11} = 1.07$	0.153	0.31
		rew - neu	$T_{66} = -2.15$	0.018	-0.26	$T_{31} = -1.02$	0.157	-0.18	$T_{15} = -1.45$	0.084	-0.36	$T_{11} = -1.49$	0.082	-0.43
		pun - neu	$T_{66} = -1.48$	0.072	-0.18	$T_{31} = -0.04$	0.485	-0.01	$T_{15} = -1.19$	0.125	-0.30	$T_{11} = -1.52$	0.078	-0.44
	Peak velocity	rew - pun	$T_{66} = -0.81$	0.209	-0.10	$T_{31} = 0.61$	0.274	0.11	$T_{15} = 0.81$	0.214	0.20	$T_{11} = -1.19$	0.130	-0.34
		rew - neu	$T_{66} = 0.00$	0.499	0.00	$T_{31} = 1.18$	0.124	0.21	$T_{15} = -0.47$	0.322	-0.12	$T_{11} = -1.45$	0.087	-0.42
		pun - neu	$T_{66} = 0.92$	0.179	0.11	$T_{31} = 0.54$	0.298	0.09	$T_{15} = -1.58$	0.067	-0.40	$T_{11} = 0.97$	0.177	0.28
	Saccade amplitude	rew - pun	$T_{66} = -0.31$	0.378	-0.04	$T_{31} = 1.28$	0.104	0.23	$T_{15} = -0.70$	0.247	-0.18	$T_{11} = -1.40$	0.094	-0.40
		rew - neu	$T_{66} = -0.45$	0.329	-0.05	$T_{31} = 0.14$	0.446	0.02	$T_{15} = 0.45$	0.330	0.11	$T_{11} = -1.58$	0.072	-0.45
		pun - neu	$T_{66} = -0.14$	0.445	-0.02	$T_{31} = -0.55$	0.293	-0.10	$T_{15} = 1.53$	0.073	0.38	$T_{11} = 0.19$	0.425	0.06
antisaccade direction errors	Frequency	rew - pun	$T_{66} = 0.21$	0.417	0.03	$T_{31} = 0.51$	0.307	0.09	$T_{15} = -0.30$	0.385	-0.07	$T_{11} = 0.30$	0.385	0.09
		rew - neu	$T_{66} = -3.35$	0.001	-0.41	$T_{31} = -3.09$	0.002	-0.55	$T_{15} = -1.05$	0.155	-0.26	$T_{11} = -0.68$	0.257	-0.19
		pun - neu	$T_{66} = -3.47$	0.000	-0.42	$T_{31} = -3.41$	0.001	-0.60	$T_{15} = -0.77$	0.227	-0.19	$T_{11} = -0.75$	0.236	-0.22
	Latency	rew - pun	$T_{61} = 1.79$	0.039	0.23	$T_{30} = 1.98$	0.029	0.36	$T_{15} = 0.43$	0.335	0.11	$T_{11} = -0.47$	0.323	-0.14
		rew - neu	$T_{64} = 3.07$	0.002	0.38	$T_{31} = 2.43$	0.010	0.43	$T_{15} = 1.70$	0.055	0.42	$T_{11} = -0.27$	0.397	-0.08
		pun - neu	$T_{62} = 0.79$	0.216	0.10	$T_{30} = 0.13$	0.448	0.02	$T_{15} = 1.09$	0.146	0.27	$T_{11} = 0.33$	0.375	0.09
	Peak velocity	rew - pun	$Z = -0.82$	0.207		$Z = -1.67$	0.048		$T_{15} = -1.04$	0.157	-0.26	$T_{11} = 0.84$	0.208	0.24
		rew - neu	$Z = -2.18$	0.015		$Z = -2.15$	0.016		$T_{15} = -0.02$	0.492	-0.01	$T_{11} = 0.62$	0.275	0.18
		pun - neu	$Z = -0.30$	0.383		$Z = -0.05$	0.480		$T_{15} = 0.68$	0.252	0.17	$T_{11} = -0.29$	0.390	-0.08
corrective saccades	Frequency	rew - pun	$T_{61} = -0.05$	0.480	-0.01	$T_{30} = 0.28$	0.391	0.05	$T_{15} = -0.75$	0.234	-0.19	$T_{11} = 0.66$	0.261	0.19
		rew - neu	$T_{64} = 0.62$	0.268	0.08	$T_{31} = 0.50$	0.310	0.09	$T_{15} = 1.27$	0.112	0.32	$T_{11} = -1.30$	0.110	-0.38
		pun - neu	$T_{62} = 1.30$	0.099	0.16	$T_{30} = 0.92$	0.181	0.17	$T_{15} = 2.18$	0.023	0.55	$T_{11} = -1.50$	0.081	-0.43
	Latency	rew - pun	$T_{59} = -1.77$	0.041	-0.23	$T_{28} = -0.40$	0.347	-0.07	$T_{15} = -1.72$	0.053	-0.43	$T_{11} = -1.62$	0.067	-0.47
		rew - neu	$T_{59} = -2.23$	0.015	-0.29	$T_{28} = -3.12$	0.002	-0.58	$T_{14} = -1.60$	0.066	-0.41	$T_{11} = -0.40$	0.348	-0.12
		pun - neu	$T_{59} = -0.99$	0.164	-0.13	$T_{28} = -1.76$	0.045	-0.33	$T_{14} = 0.15$	0.443	0.04	$T_{11} = 1.12$	0.144	0.32

Table 9-18: Post-hoc between-group analyses (independent-sample t-test T_{df} or Mann-Whitney-U test Z; significance p; effect size d for t-tests or θ for Mann-Whitney-U tests) for all dependant variables per saccade type explored for group differences in incentive-related modulation, per variable, incentive condition, and subject group. Significant differences ($p \leq 0.05/3 = 0.0167$) are printed in red, p =1-tailed.

Dependant Variable per Saccade Type and Incentive Condition			Adolescents – Patients with Anxiety			Adolescents – Patients with MDD			Patients with Anxiety – Patients with MDD		
			T or Z	p	d or θ	T or Z	p	d or θ	T or Z	p	d or θ
correct prosaccades	Frequency	punishment	$T_{46} = -0.38$	0.354	-0.12	$T_{42} = 0.66$	0.257	0.22	$T_{15.41} = 0.92$	0.187	0.36
		reward	$T_{46} = -1.10$	0.138	-0.33	$T_{42} = 0.00$	0.500	0.00	$T_{26} = 0.89$	0.190	0.35
		neutral	$T_{46} = -1.03$	0.155	-0.35	$T_{42} = -1.33$	0.095	-0.50	$T_{26} = -0.69$	0.249	-0.26
	Latency	punishment	$T_{46} = 1.60$	0.058	0.52	$T_{42} = 0.68$	0.250	0.21	$T_{26} = -0.48$	0.318	-0.17
		reward	$T_{46} = 1.39$	0.086	0.43	$T_{42} = 1.06$	0.148	0.35	$T_{26} = -0.15$	0.440	-0.06
		neutral	$T_{46} = 0.90$	0.185	0.29	$T_{42} = 0.31$	0.377	0.10	$T_{16.58} = -0.35$	0.366	-0.14
	Peak Velocity	punishment	$T_{46} = -0.05$	0.480	-0.02	$T_{33.29} = 0.70$	0.243	0.21	$T_{25.76} = 0.67$	0.254	0.25
		reward	$T_{46} = -0.71$	0.241	-0.20	$T_{42} = 0.03$	0.487	0.01	$T_{26} = 0.59$	0.280	0.24
		neutral	$T_{46} = -1.53$	0.066	-0.44	$T_{42} = -0.34$	0.368	-0.13	$T_{21.67} = 1.12$	0.138	0.41
	Saccade Amplitude	punishment	$T_{46} = -1.21$	0.116	-0.37	$T_{42} = -2.01$	0.026	-0.62	$T_{26} = -0.81$	0.212	-0.30
		reward	$T_{46} = -1.26$	0.106	-0.37	$T_{42} = -1.96$	0.028	-0.60	$T_{26} = -0.76$	0.226	-0.29
		neutral	$T_{46} = -2.04$	0.024	-0.61	$T_{42} = -1.83$	0.037	-0.56	$T_{26} = -0.12$	0.452	-0.04
correct antisaccades	Frequency	punishment	$T_{46} = 0.81$	0.212	0.26	$T_{42} = 1.12$	0.134	0.37	$T_{26} = 0.47$	0.322	0.17
		reward	$T_{46} = 0.56$	0.290	0.17	$T_{42} = 0.84$	0.203	0.26	$T_{26} = 0.28$	0.392	0.10
		neutral	$T_{46} = -0.64$	0.264	-0.19	$T_{42} = -0.11$	0.456	-0.04	$T_{26} = 0.41$	0.342	0.16
	Latency	punishment	$T_{46} = 0.72$	0.238	0.23	$T_{42} = 2.13$	0.020	0.63	$T_{26} = 1.40$	0.086	0.51
		reward	$T_{45} = 0.55$	0.293	0.16	$T_{42} = 0.59$	0.279	0.19	$T_{26} = 0.08$	0.469	0.03
		neutral	$T_{46} = 0.15$	0.441	0.05	$T_{42} = -0.89$	0.190	-0.26	$T_{26} = -0.81$	0.212	-0.29
	Peak Velocity	punishment	$T_{46} = -0.38$	0.353	-0.12	$T_{11.95} = -1.11$	0.145	-0.44	$T_{26} = -1.08$	0.146	-0.38
		reward	$T_{30.08} = -0.62$	0.269	-0.19	$T_{37.70} = 1.09$	0.142	0.32	$T_{22.48} = 1.43$	0.083	0.52
		neutral	$T_{46} = -1.68$	0.050	-0.51	$T_{42} = -1.31$	0.099	-0.44	$T_{26} = 0.17$	0.435	0.06
	Saccade Amplitude	punishment	$T_{45} = -1.55$	0.064	-0.46	$T_{42} = -1.88$	0.033	-0.55	$T_{26} = -0.55$	0.293	-0.20
		reward	$T_{46} = -0.64$	0.262	-0.20	$T_{42} = 0.05$	0.479	0.02	$T_{21.46} = 0.76$	0.227	0.27
		neutral	$T_{46} = -0.53$	0.299	-0.17	$T_{42} = -1.20$	0.119	-0.42	$T_{26} = -0.86$	0.200	-0.32
antisaccade direction errors	Frequency	punishment	$T_{46} = -0.71$	0.241	-0.22	$T_{42} = -0.91$	0.184	-0.30	$T_{26} = -0.32$	0.377	-0.12
		reward	$T_{46} = -0.44$	0.330	-0.13	$T_{42} = -1.11$	0.137	-0.34	$T_{26} = -0.60$	0.276	-0.23
		neutral	$T_{46} = 0.46$	0.324	0.14	$T_{42} = 0.10$	0.462	0.03	$T_{26} = -0.29$	0.386	-0.11
	Latency	punishment	$T_{45} = 0.20$	0.421	0.06	$T_{41} = 0.64$	0.263	0.22	$T_{26} = 0.38$	0.352	0.15
		reward	$T_{46} = 1.10$	0.138	0.37	$T_{42} = 1.75$	0.044	0.67	$T_{26} = 1.10$	0.140	0.42
		neutral	$T_{46} = 1.03$	0.154	0.33	$T_{42} = 0.57$	0.284	0.20	$T_{26} = -0.34$	0.367	-0.13
	Peak Velocity	punishment	$Z = -0.82$	0.206	0.43	$Z = -0.07$	0.473	0.49	$T_{26} = 0.74$	0.234	0.29
		reward	$Z = -0.51$	0.304	0.45	$Z = -0.08$	0.468	0.49	$T_{26} = -0.42$	0.339	-0.16
		neutral	$Z = -0.46$	0.323	0.46	$Z = -0.95$	0.171	0.41	$T_{26} = -0.02$	0.492	-0.01
	Saccade Amplitude	punishment	$Z = -0.09$	0.464	0.49	$Z = -1.07$	0.142	0.39	$T_{26} = -1.05$	0.153	-0.39
		reward	$Z = -0.43$	0.335	0.46	$Z = -1.17$	0.120	0.38	$T_{14.68} = -1.71$	0.054	-0.69
		neutral	$Z = -0.67$	0.252	0.44	$Z = -1.12$	0.131	0.39	$T_{26} = -1.70$	0.051	-0.63
corrective saccades	Frequency	punishment	$T_{45} = -2.62$	0.006	-0.73	$T_{41} = -0.50$	0.311	-0.17	$T_{16.1} = 1.41$	0.086	0.56
		reward	$T_{46} = -1.39$	0.086	-0.45	$T_{42} = -1.05$	0.149	-0.39	$T_{26} = 0.22$	0.414	0.08
		neutral	$T_{46} = -0.59$	0.279	-0.18	$T_{42} = -1.85$	0.035	-0.68	$T_{26} = -1.18$	0.125	-0.46
	Latency	punishment	$T_{44} = -0.46$	0.325	-0.16	$T_{40} = -1.18$	0.123	-0.41	$T_{26} = -0.57$	0.285	-0.20
		reward	$T_{44} = 1.12$	0.134	0.34	$T_{40} = 0.33$	0.372	0.07	$T_{26} = -0.60$	0.278	-0.28
		neutral	$T_{44} = 1.61$	0.057	0.56	$T_{41} = 1.18$	0.123	0.43	$T_{26} = -0.19$	0.427	-0.05
	Peak Velocity	punishment	$Z = -0.85$	0.109	0.42	$Z = -0.21$	0.417	0.48	$T_{26} = 1.19$	0.122	0.48
		reward	$Z = -0.21$	0.418	0.48	$Z = -0.33$	0.369	0.47	$T_{26} = 0.43$	0.335	0.16
		neutral	$Z = -1.11$	0.133	0.40	$Z = -1.68$	0.047	0.33	$T_{20.76} = 0.32$	0.374	0.13
	Saccade Amplitude	punishment	$T_{44} = -0.31$	0.379	-0.09	$T_{40} = -0.94$	0.176	-0.30	$T_{26} = -0.58$	0.283	-0.22
		reward	$T_{44} = 0.87$	0.194	0.27	$T_{40} = -1.04$	0.151	-0.39	$T_{26} = -1.94$	0.032	-0.72
		neutral	$T_{44} = -1.78$	0.041	-0.48	$T_{41} = -0.91$	0.184	-0.32	$T_{26} = 0.80$	0.215	0.32

9.6.3 Outcome notification period

Table 9-19: Summary of main effects and interactions ($F_{df/dferror}$, p) of the Analysis of Variance for each dependant variable analyzed during the outcome notification period. Significant differences ($p \leq 0.05$) are printed in red.

Dependant Variable per Condition	Feedback	Feedback by Diagnosis	Incentives	Incentives by Diagnosis	Feedback by Incentives	Feedback by Incentives by Diagnosis	Diagnosis
Fixation Duration	$F_{1,57} = 6.49$ $p = 0.014$	$F_{2,57} = 0.42$ $p = 0.657$	$F_{2,56} = 2.77$ $p = 0.071$	$F_{2,57} = 2.19$ $p = 0.121$	$F_{2,56} = 1.74$ $p = 0.186$	$F_{2,57} = 3.11$ $p = 0.052$	$F_{2,57} = 0.95$ $p = 0.392$
Pupil Diameter	$F_{1,57} = 80.63$ $p = 0.000$	$F_{2,57} = 1.04$ $p = 0.360$	$F_{2,56} = 10.68$ $p = 0.000$	$F_{2,57} = 0.87$ $p = 0.423$	$F_{2,56} = 0.01$ $p = 0.988$	$F_{2,57} = 0.89$ $p = 0.417$	$F_{2,57} = 2.87$ $p = 0.065$
Pupil Dilation	$F_{1,57} = 26.38$ $p = 0.000$	$F_{2,57} = 1.02$ $p = 0.368$	$F_{2,56} = 2.55$ $p = 0.087$	$F_{2,57} = 1.85$ $p = 0.166$	$F_{2,56} = 6.27$ $p = 0.003$	$F_{2,57} = 0.89$ $p = 0.416$	$F_{2,57} = 2.44$ $p = 0.096$

Table 9-20: Post-hoc within-group analysis (paired-sample t-test T_{df}; significance p; effect size d_z) for all dependant variables showing an incentive-related modulation in the Analysis of Variance, per feedback type, within-group comparison, and subject group. Significant differences ($p \leq 0.05/3 = 0.0167$) are printed in red, p =1-tailed. rew = reward condition, pun = punishment condition; neu = neutral condition.

Comparison between Incentive Conditions per Feedback Type and Dependant Variable			All subjects			Adolescents			Patients with Anxiety			Patients with MDD		
			T	p	d_z	T	p	d_z	T	p	d_z	T	p	d_z
Fixation Duration	Positive Feedback	rew - pun	$T_{66} = -0.07$	0.470	-0.01	$T_{31} = 0.99$	0.166	0.17	$T_{15} = -0.64$	0.265	-0.16	$T_{11} = -0.69$	0.253	-0.20
		rew - neu	$T_{66} = 0.60$	0.276	0.07	$T_{31} = -0.20$	0.421	-0.04	$T_{15} = 1.17$	0.130	0.29	$T_{11} = -0.40$	0.349	-0.12
		pun - neu	$T_{66} = 0.66$	0.257	0.08	$T_{31} = -1.33$	0.097	-0.23	$T_{15} = 1.31$	0.105	0.33	$T_{11} = 0.55$	0.297	0.16
	Negative Feedback	rew - pun	$T_{66} = -1.31$	0.097	-0.16	$T_{31} = -0.72$	0.238	-0.13	$T_{15} = 0.21$	0.417	0.05	$T_{11} = -1.94$	0.039	-0.56
		rew - neu	$T_{66} = 0.85$	0.200	0.10	$T_{31} = -0.09$	0.463	-0.02	$T_{15} = 0.67$	0.258	0.17	$T_{11} = 0.16$	0.436	0.05
		pun - neu	$T_{66} = 2.43$	0.009	0.30	$T_{31} = 0.84$	0.205	0.15	$T_{15} = 0.34$	0.369	0.09	$T_{11} = 2.93$	0.007	0.84
	Feedback Combined	rew - pun	$T_{66} = -0.88$	0.190	-0.11	$T_{31} = 0.36$	0.362	0.06	$T_{15} = -0.96$	0.177	-0.24	$T_{11} = -1.04$	0.159	-0.30
		rew - neu	$T_{66} = 0.73$	0.234	0.09	$T_{31} = -0.11$	0.458	-0.02	$T_{15} = 0.78$	0.225	0.19	$T_{11} = 0.11$	0.458	0.03
		pun - neu	$T_{66} = 1.54$	0.064	0.19	$T_{31} = -0.47$	0.321	-0.08	$T_{15} = 1.16$	0.133	0.29	$T_{11} = 2.08$	0.031	0.60
Pupil Diameter	Positive Feedback	rew - pun	$T_{66} = 1.92$	0.029	0.23	$T_{31} = 1.37$	0.091	0.24	$T_{15} = 0.17$	0.433	0.04	$T_{11} = 1.58$	0.071	0.46
		rew - neu	$T_{66} = 4.83$	0.000	0.59	$T_{31} = 2.80$	0.004	0.49	$T_{15} = 4.57$	0.000	1.14	$T_{11} = 1.76$	0.053	0.51
		pun - neu	$T_{66} = 3.53$	0.000	0.43	$T_{31} = 1.89$	0.034	0.33	$T_{15} = 3.39$	0.002	0.85	$T_{11} = 0.89$	0.197	0.26
	Negative Feedback	rew - pun	$T_{66} = 0.45$	0.327	0.05	$T_{31} = 0.22$	0.413	0.04	$T_{15} = 0.06$	0.475	0.02	$T_{11} = 0.76$	0.233	0.22
		rew - neu	$T_{66} = 4.34$	0.000	0.53	$T_{31} = 3.34$	0.001	0.59	$T_{15} = 1.96$	0.035	0.49	$T_{11} = 1.16$	0.136	0.33
		pun - neu	$T_{66} = 3.51$	0.000	0.43	$T_{31} = 2.29$	0.014	0.40	$T_{15} = 2.60$	0.010	0.65	$T_{11} = 0.14$	0.444	0.04
	Feedback Combined	rew - pun	$T_{66} = 0.72$	0.237	0.09	$T_{31} = 0.69$	0.246	0.12	$T_{15} = -0.55$	0.295	-0.14	$T_{11} = 0.87$	0.201	0.25
		rew - neu	$T_{66} = 5.41$	0.000	0.66	$T_{31} = 3.29$	0.001	0.58	$T_{15} = 4.28$	0.000	1.07	$T_{11} = 2.09$	0.031	0.60
		pun - neu	$T_{66} = 4.44$	0.000	0.54	$T_{31} = 2.63$	0.007	0.47	$T_{15} = 3.82$	0.001	0.96	$T_{11} = 1.19$	0.130	0.34
Pupil Dilation	Positive Feedback	rew - pun	$T_{66} = 2.20$	0.016	0.27	$T_{31} = 1.30$	0.101	0.23	$T_{15} = 1.14$	0.137	0.28	$T_{11} = 0.75$	0.236	0.22
		rew - neu	$T_{66} = -0.26$	0.396	-0.03	$T_{31} = -1.29$	0.104	-0.23	$T_{15} = 0.56$	0.290	0.14	$T_{11} = -0.25$	0.404	-0.07
		pun - neu	$T_{66} = -1.89$	0.032	-0.23	$T_{31} = -2.07$	0.024	-0.37	$T_{15} = -0.24$	0.407	-0.06	$T_{11} = -0.79$	0.222	-0.23
	Negative Feedback	rew - pun	$T_{66} = 0.78$	0.218	0.10	$T_{31} = 0.10$	0.462	0.02	$T_{15} = 2.20$	0.022	0.55	$T_{11} = 0.05$	0.481	0.01
		rew - neu	$T_{66} = 2.44$	0.009	0.30	$T_{31} = 0.96$	0.173	0.17	$T_{15} = 2.25$	0.020	0.56	$T_{11} = 1.74$	0.055	0.50
		pun - neu	$T_{66} = 1.44$	0.078	0.18	$T_{31} = 0.70$	0.244	0.12	$T_{15} = 0.49$	0.317	0.12	$T_{11} = 1.42$	0.091	0.41
	Feedback Combined	rew - pun	$T_{66} = 2.21$	0.015	0.27	$T_{31} = 0.91$	0.184	0.16	$T_{15} = 2.29$	0.018	0.57	$T_{11} = 0.34$	0.371	0.10
		rew - neu	$T_{66} = 0.73$	0.233	0.09	$T_{31} = -0.56$	0.290	-0.10	$T_{15} = 1.39$	0.093	0.35	$T_{11} = 0.38$	0.357	0.11
		pun - neu	$T_{66} = -1.26$	0.106	-0.15	$T_{31} = -1.44$	0.079	-0.26	$T_{15} = -0.66$	0.260	-0.16	$T_{11} = 0.07$	0.472	0.02

10. Appendix III: Figures

10.1 Accuracy Scenarios

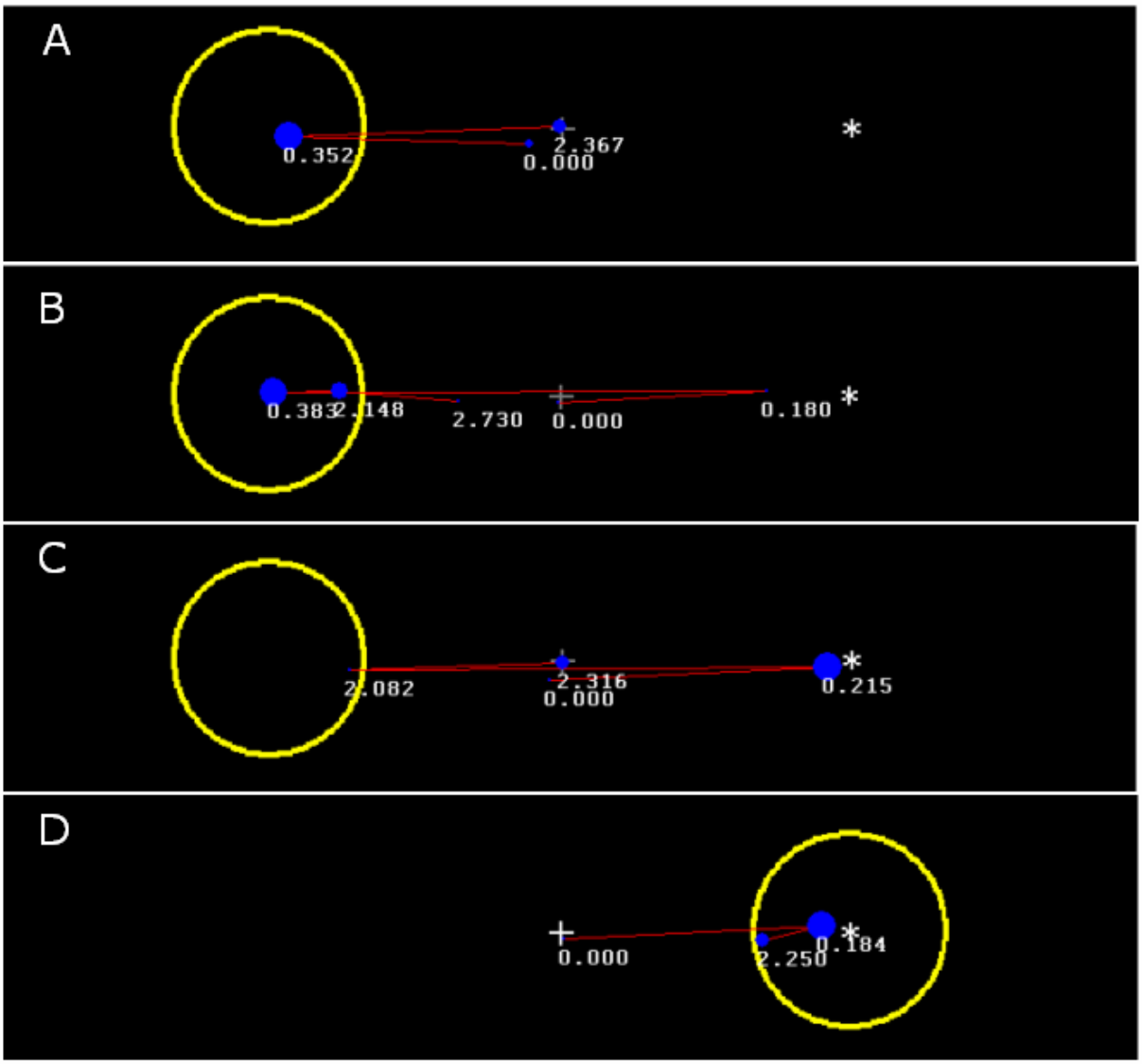

Figure 10-1: A) Correct antisaccade: Subject gazed at the correct location with a latency of 352ms after target onset. B) Corrected direction error: Subject looked at the target instead of its mirror location within 180ms after target onset and re-located its gaze to the correct position within 382ms after target onset. While this trial was considered a direction error in the analysis, it was considered a correct outcome during the task since the gaze was located at the correct position within 500ms after target onset. C) Direction error: Subject looked at the target instead of its mirror location within 215ms after target onset and remained there until appearance of feedback (2.082s after target onset). D) Correct prosaccade: Subject gazed at the place where the target appeared within 184ms after target onset The size of the blue dot represents fixation duration; yellow circles demark the area in which a gaze was considered correct by the task computer.

10.2 Saccadic Reaction Time Distributions

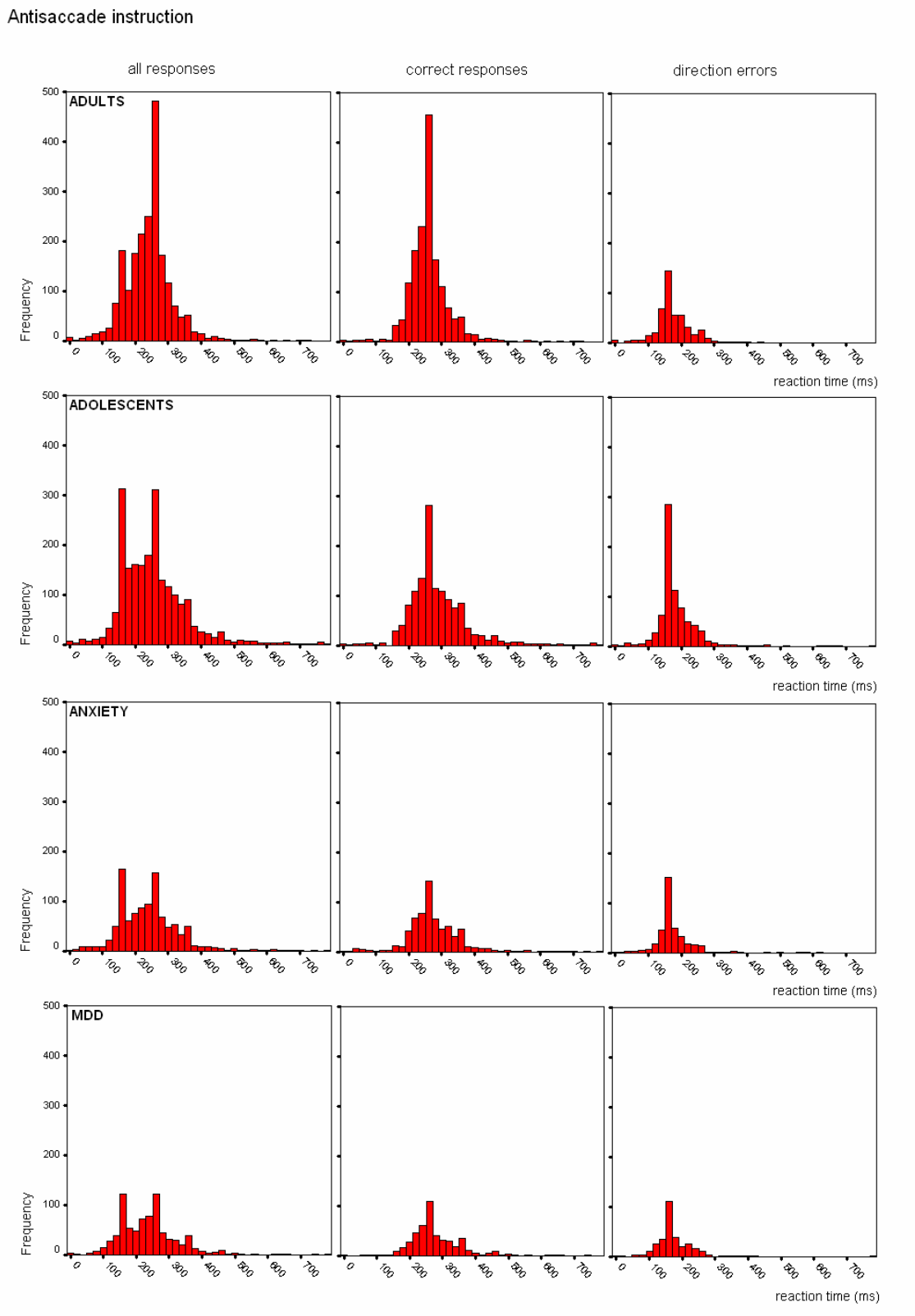

Figure 10-2: Saccade reaction time distributions of all saccades with amplitudes between 1.5° and 17° visual angle that were directed either to the left or right side of the screen, during the antisaccade instruction for all diagnostic groups: Top panel shows latencies of adults, the upper middle panel control of adolescents, the lower middle panel of adolescents with anxiety disorders, and the bottom panel of adolescents with MDD. The left hand side row shows all responses recorded, the middle row all correct responses recorded, and the right hand side row all direction errors recorded. Of note there were fewer subjects in the two clinical groups and thus overall less data available.

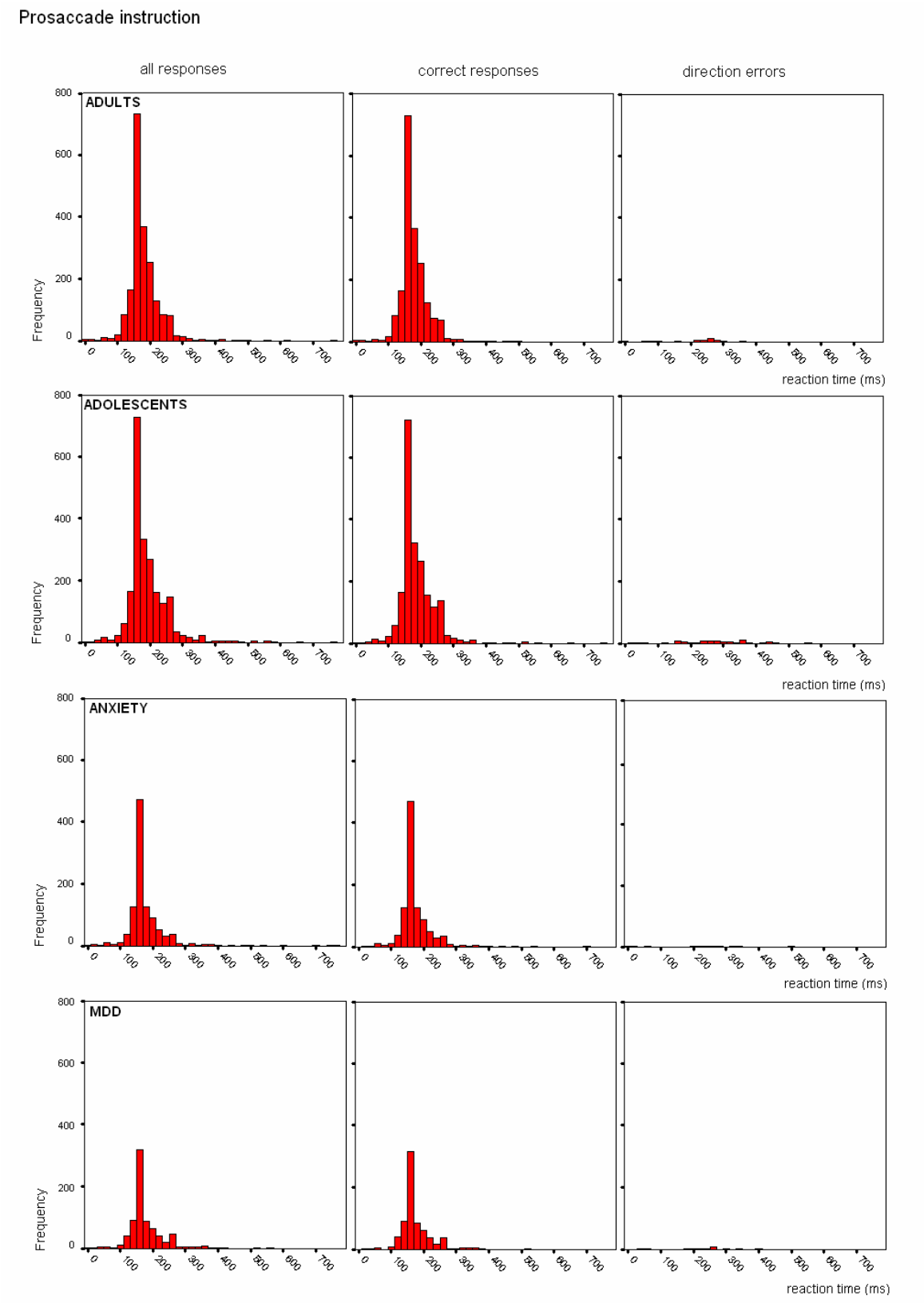

Figure 10-3: Saccade reaction time distributions of all saccades with amplitudes between 1.5° and 17° visual angle that were directed either to the left or right side of the screen, during the prosaccade instruction for all diagnostic groups: Top panel shows latencies of adults, the upper middle panel control of adolescents, the lower middle panel of adolescents with anxiety disorders, and the bottom panel of adolescents with MDD. The left hand side row shows all responses recorded, the middle row all correct responses recorded, and the right hand side row all direction errors recorded. Of note there were fewer subjects in the two clinical groups and thus overall less data available.

10.3 Figures Developmental Study

10.3.1 Self-Reports

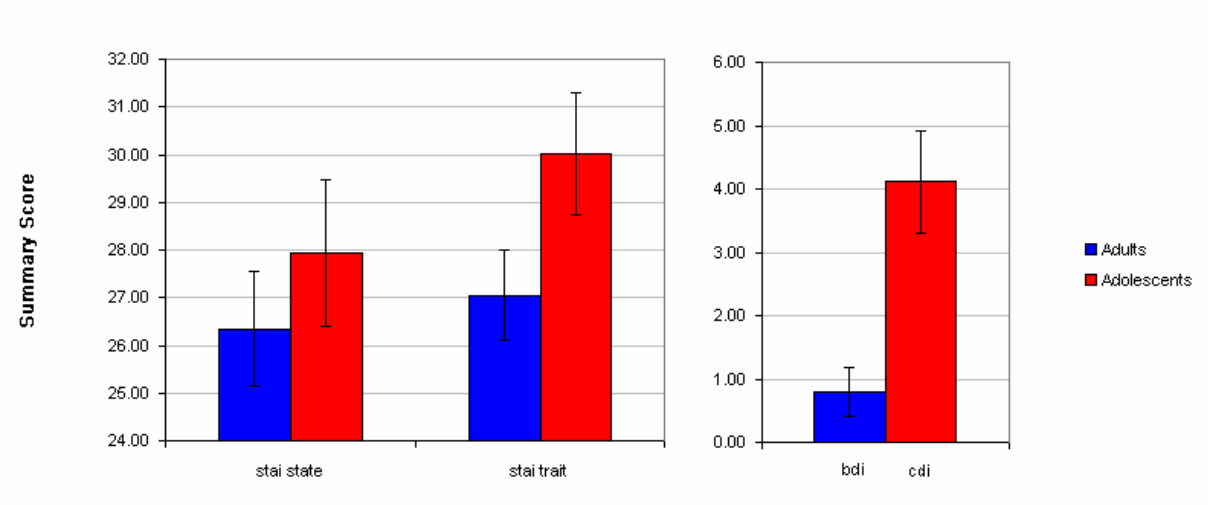

Figure 10-4: Summary scores (mean ± SE) of self –reports administered before eye movement testing (stai state = Spielberg State-Trait Anxiety Inventory state form; stai trait = Spielberg State-Trait Anxiety Inventory trait from; bdi = Beck Depression Inventory (administered to adults) and cdi = Children Depression Inventory (administered to adolescents)) per age group (red = adolescents; blue = adults).

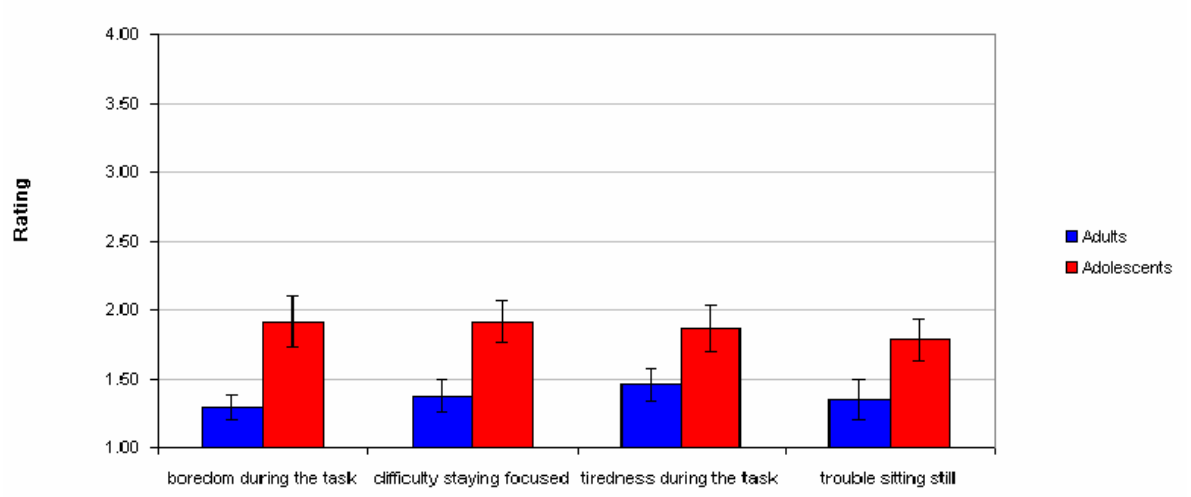

Figure 10-5: Ratings on items of the Debriefing Questionnaire for which there were significant differences between age groups (red = adolescents; blue = adults).

10.3.2 Performance Period

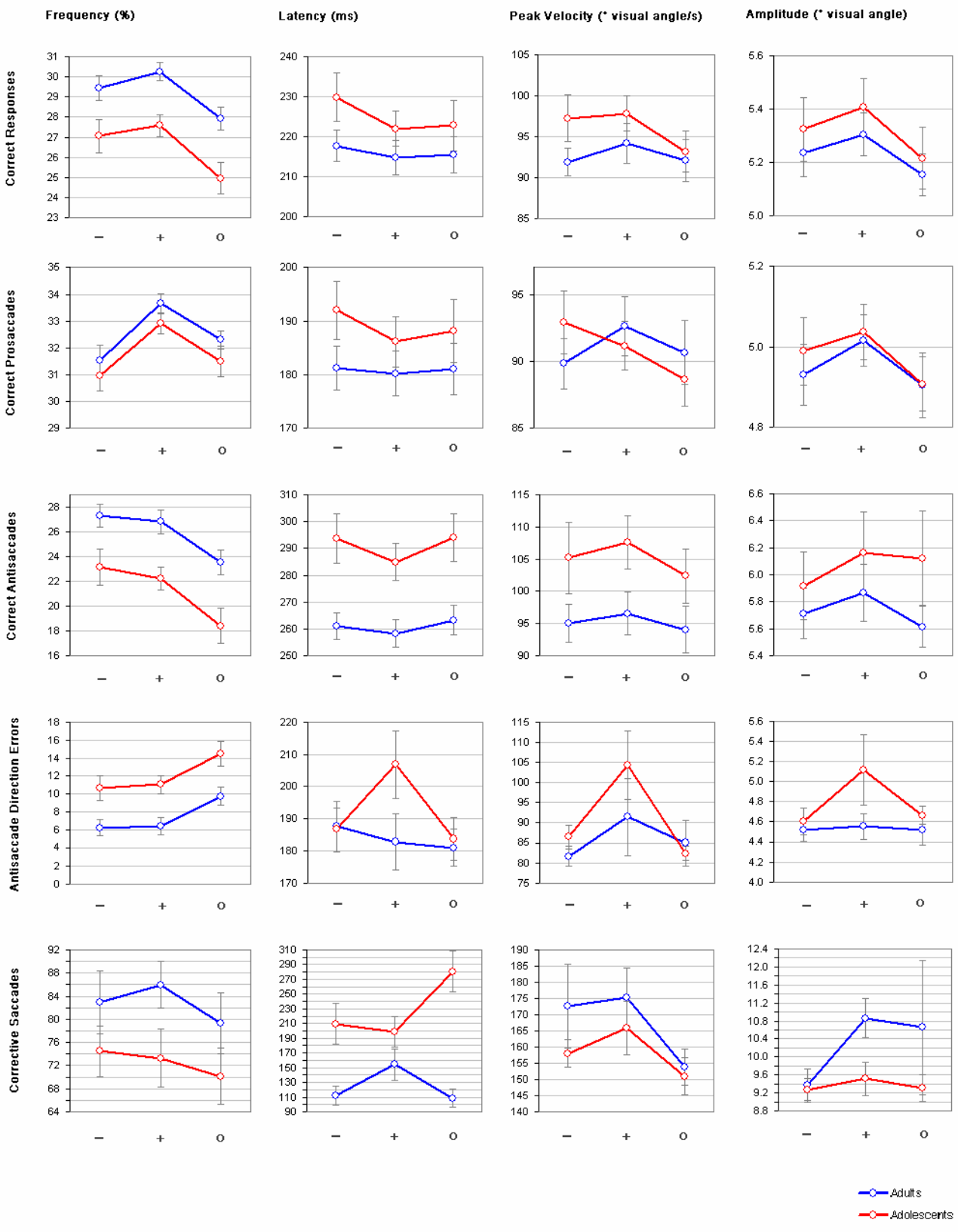

Figure 10-6: Incentive-related modulation of dependant variables (mean ± SE) during the performance period of the RST per condition ("-" = punishment condition; "+" = reward condition; "o" = neutral condition), per saccade type analyzed, and per age group (red = adolescents, blue = adults).

10.3.3 Outcome Notification Period

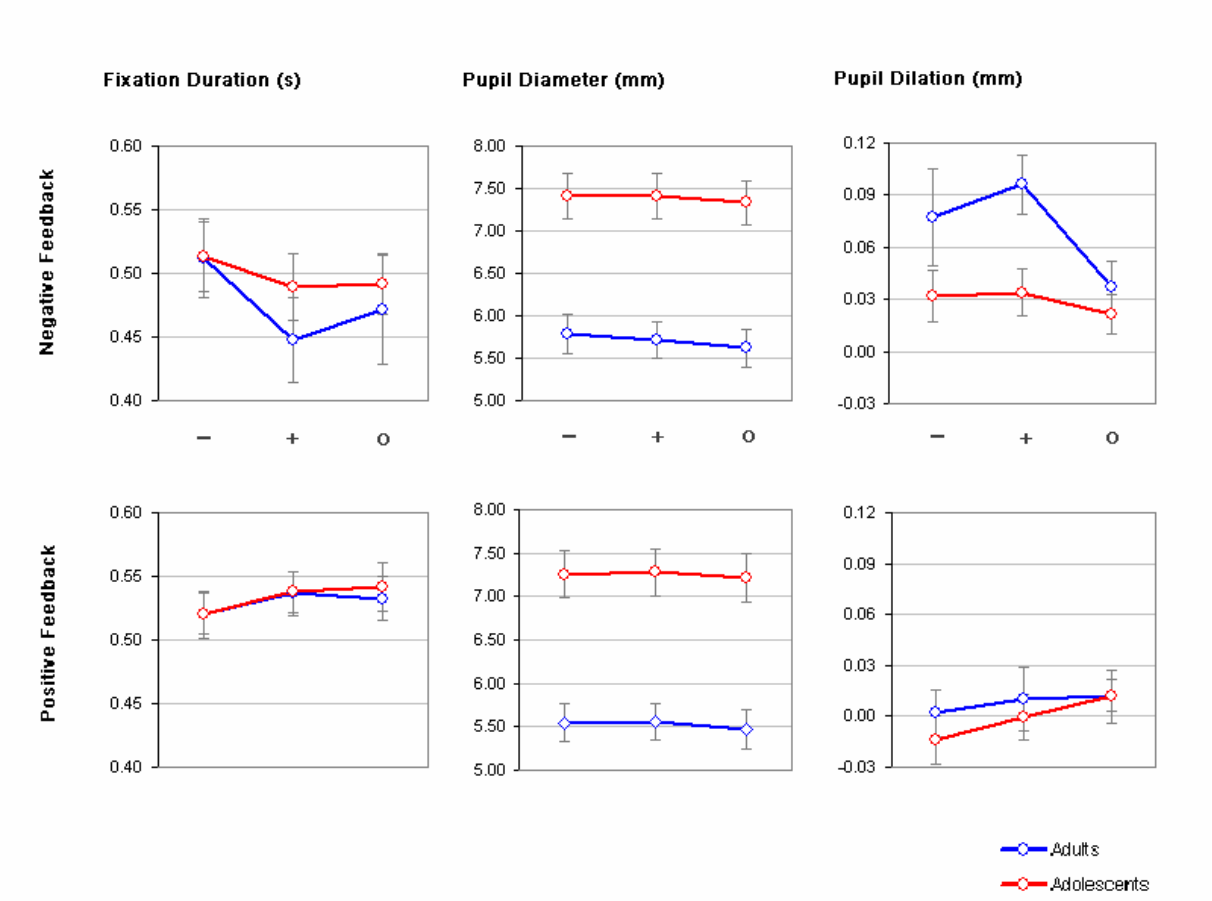

Figure 10-7: Incentive-related modulation of dependant variables (mean ± SE) during the outcome notification period of the RST per incentive condition ("-" = punishment condition; "+" = reward condition; "o" = neutral condition), per feedback type (positive = win money for the reward condition, avoid losing money for the punishment condition, or feedback of correct performance for the neutral condition; negative = not winning money for the reward condition, losing money for the punishment condition, or feedback of incorrect performance for the neutral condition), and per age group (red = adolescents, blue = adults).

10.4 Figures Clinical Study

10.4.1 Self-Reports

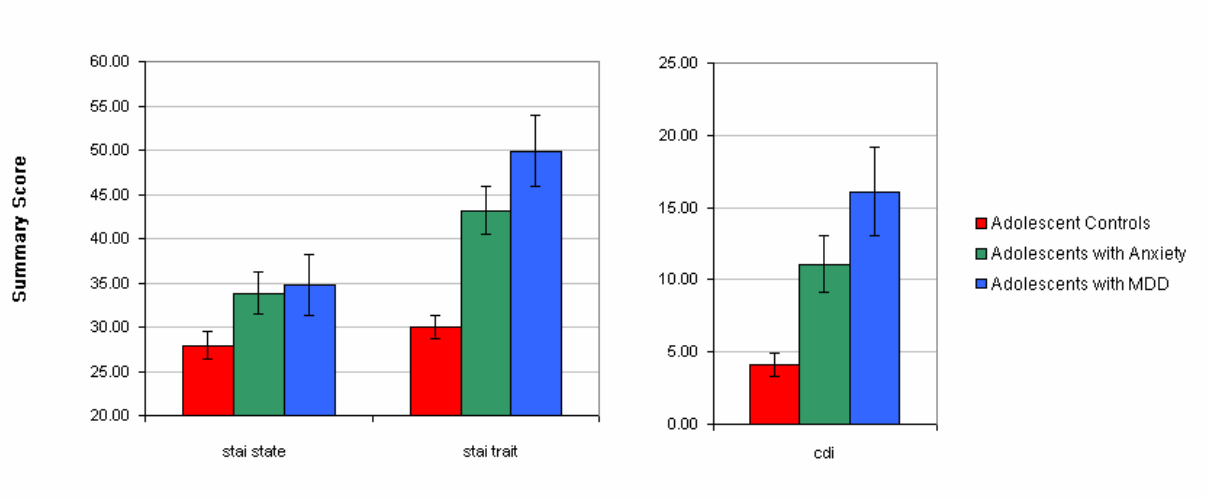

Figure 10-8: Summary scores (mean ± SE) of self –reports administered before eye movement testing (stai state = Spielberg State-Trait Anxiety Inventory state form; stai trait = Spielberg State-Trait Anxiety Inventory trait from; cdi = Children Depression Inventory) per diagnostic group (red = adolescent controls; green = adolescents with an anxiety disorders; light blue = adolescents with MDD).

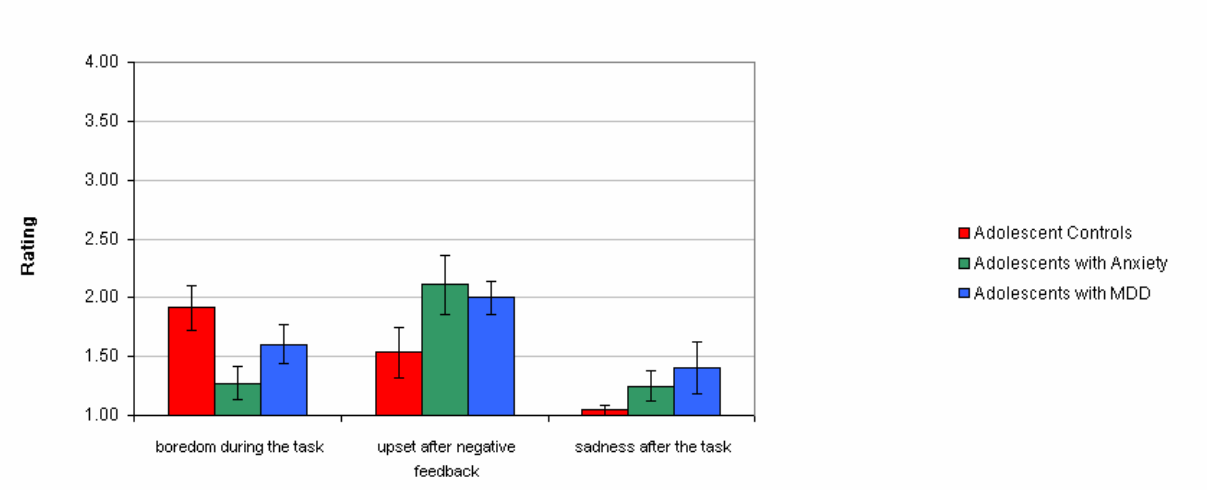

Figure 10-9: Ratings on items of the Debriefing Questionnaire for which there were trends for differences between diagnostic groups (red = adolescent controls; green = adolescents with an anxiety disorders; light blue = adolescents with MDD).

10.4.2 Performance Period

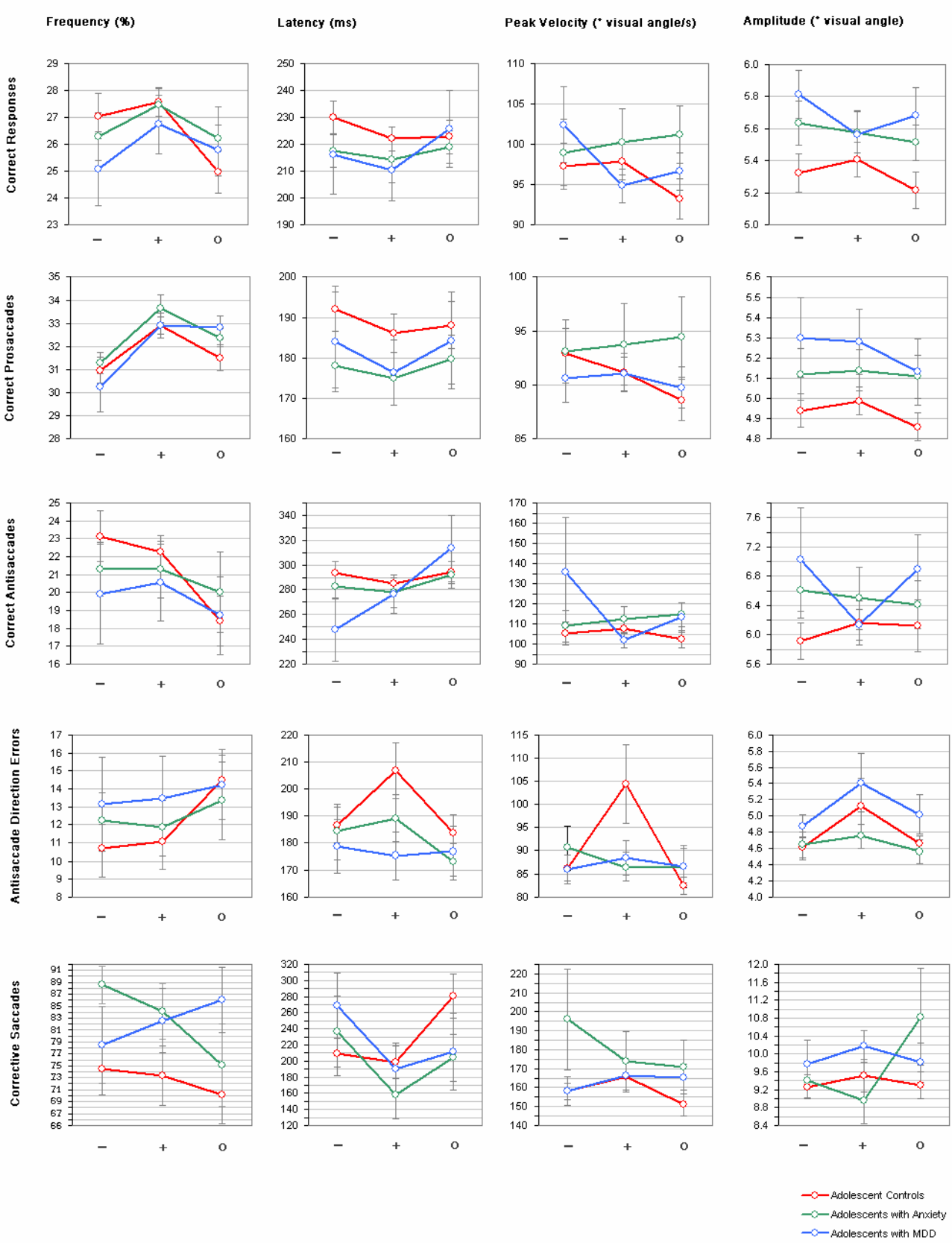

Figure 10-10: Incentive-related modulation of dependant variables (mean ± SE) during the performance period of the RST per condition ("-" = punishment condition; "+" = reward condition; "o" = neutral condition), per saccade type analyzed, and per diagnostic group (red = adolescents, green = adolescents with Anxiety; light blue = adolescents with MDD).

10.4.3 Outcome Notification Period

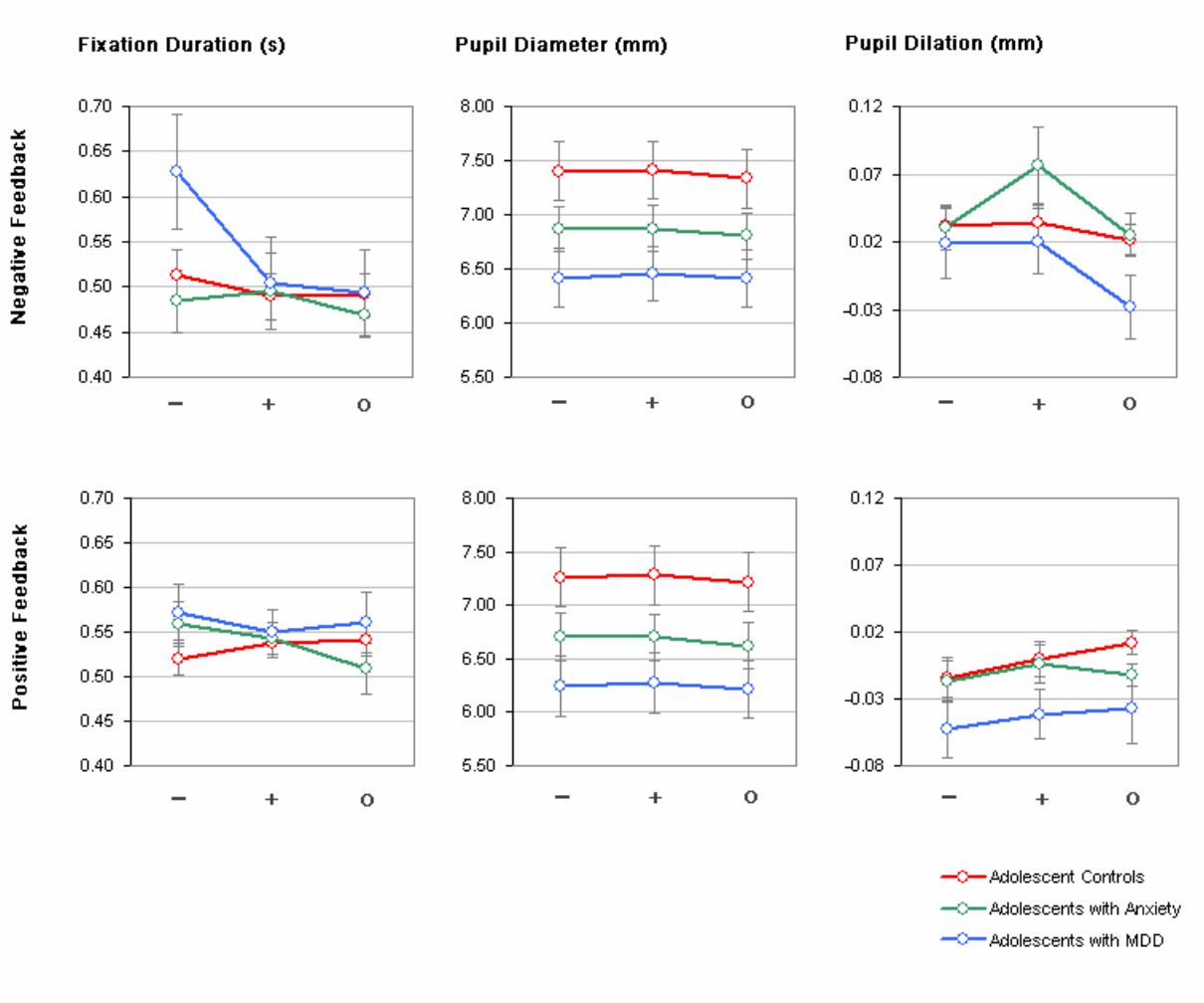

Figure 10-11: Incentive-related modulation of dependant variables (mean ± SE) during the outcome notification period of the RST per incentive condition ("-" = punishment condition; "+" = reward condition; "o" = neutral condition), per feedback type (positive = win money for the reward condition, avoid losing money for the punishment condition, or feedback of correct performance for the neutral condition; negative = not winning money for the reward condition, losing money for the punishment condition, or feedback of incorrect performance for the neutral condition), and per diagnostic group (red = adolescents, green = adolescents with Anxiety; light blue = adolescents with MDD).

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